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(54) NOVEL PROTEIN AND METHODS FOR THE PRODUCTION OF THE SAME

(57) A protein which inhibits osteoclast differentiation and/or maturation and a method of production of the protein. The protein is produced by human embryonic lung fibroblasts and has molecular weight of about 60 kD and about 120 kD under non-reducing conditions and about 60 kD under reducing conditions on SDS-polyacrylamide gel electrophoresis, respectively.

The protein can be isolated and purified from culture medium of the said fibroblasts. Furthermore, the protein can be produced by gene engineering.

The present invention includes cDNA for producing the protein by gene engineering, antibodies having specific affinity to the protein or a method for determination of the protein concentration using the antibodies.

Description

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Field of the invention

This invention relates to a novel protein, osteoclastogenesis inhibitory factor (OCIF), and methods for producing the 5 protein.

Background of the invention

Human bones are always remodelling by the repeated process of resorption and reconstitution. In the process, osteoblasts and osteoclasts are considered to be the cells mainly responsible for bone formation and bone resorption, respectively. A typical example of disease caused by the progression of abnormal bone metabolism is osteoporosis. The disease is known to be provoked by the condition in which bone resorption by osteoclasts exceeds bone formation by osteoblasts, but the mechanism of osteoporosis has not yet been completely elucidated. Osteoporosis causes pain in the bone and makes the bone fragile, leading to fracture. Since osteoporosis increases the number of bedridden old people, it has become a social issue with the increasing number of old people. Therefore, efficacious drugs for the treatment of the disease are expected to be developed. Bone mass reduction caused by the abnormal bone metabolism is thought to be prevented by inhibiting bone resorption, improving bone formation, or improving the balanced metabo-

Bone formation is expected to be promoted by stimulating growth, differentiation, or activation of osteoblasts. Many cytokines are reported to stimulate growth or differentation of osteoblasts, i.e. fibroblast growth factor (FGF) (Rodan S. B. et al., Endocrinology vol. 121, p1917, 1987), insulin-like growth factor-I (IGF-I) (Hock J.M. et al., Endocrinology vol. 122, p254, 1988), insulin-like growth factor-II (IGF-II) (McCarthy T. et al., Endocrinology vol. 124, p301, 1989), Activin A (Centrella M. et al., Mol, Cell, Biol. vol. 11, p250, 1991), Vasculotropin (Varonique M et al., Biochem. Biophys. Res. 25 Commun. vol. 199, p380, 1994), and bone morphogenetic protein (BMP) (Yamaguchi, A et al., J. Cell Biol. vol. 113, p682, 1991, Sampath T.K. et al., J. Biol Chem. vol.267, p20532, 1992, and Knutsen R. et al., Biochem. Biophys. Res. Commun. vol.194, p1352, 1993.

On the other hand, cytokines which inhibits differentiation and/or maturation of osteoclasts have been paid attention and have been intensively studied. Transforming growth factor-β (Chenu C. et al., Proc. Natl. Acad. Sci. USA, vol.85, p5683, 1988) and interleukin-4 (Kasano K. et al., Bone-Miner., vol. 21, p179, 1993) are found to inhibit the differentiation of osteoclasts. Calcitonin (Bone-Miner., vol.17, p347, 1992), Macrophage colony-stimulating factor (Hattersley G. et al. J. Cell. Physiol. vol.137, p199, 1988), interleukin-4 (Watanabe, K. et al., Biochem. Biophys. Res. Commun. vol. 172, p1035, 1990), and interferon-γ (Gowen M. et al., J. Bone Miner. Res., vol.1, p469, 1986) are found to inhibit bone resorption by osteoclasts.

These cytokines are expected to be efficacious drugs for improving bone mass reduction by stimulating bone formation and/or by inhibiting bone resorption. The cytokines such as insulin like growth factor-I and bone morphogenetic proteins are now investigated in clinical trials for their effects in treatment of patients with bone diseases. Calcitonin is already used as a drug to care osteoporosis and to diminish pain in osteoporosis.

Examples of drugs now clinically utilized for the treatment of bone diseases and for shortening the treatment period are dihydroxyvitamine D_3 , vitamin K_2 , calcitonin and its derivatives, hormones such as estradiol, ipriflavon, and calcium preparations. However, these drugs do not provide satisfactory therapeutic effects, and novel drug substances have been expected to be developed. As mentioned, bone metabolism is controlled in the balance between bone resorption and bone formation. Therefore, cytokines which inhibit osteoclast differentiation and/or maturation are expected to be developed as drugs for the treatment of bone diseases such as osteoporosis.

Disclosure of Invention

This invention was initiated from the view point described above. The purpose of this invention is to offer both a novel factor termed osteoclastogenesis inhibitory factor (OCIF) and a procedure to produce the factor efficiently.

The inventors have intensively searched for osteoclastogenesis inhibitory factors in human embryonic fibloblast IMR-90 (ATCC CCL186) conditioned medium and have found a novel osteoclastogenesis inhibitory factor (OCIF) which inhibits differentiation and/or maturation of osteoclasts.

The inventors have established a method for accumulating the protein to a high concentration by culturing IMR-90 cells using alumina ceramic pieces as the cell adherence matrices.

The inventors have also established an efficient method for isolating the protein, OCIF, from the IMR-90 conditioned medium using the following sequential column chromatography, ion-exchange, heparin affinity, cibacron-blue affinity, and reverse phase.

The inventors, based on the amino acid sequence of the purified natural OCIF, successfully cloned a cDNA encod-

ing this protein. The inventors established also a procedure to produce this protein which inhibits differentiation of osteoclasts. This invention concerns a protein which is produced by human lung fibroblast cells, has molecular weights in SDS-PAGE of 60 KD in the reducing conditions and 120 KD under the non-reducing conditions, has affinity for both cation-exchange resins and heparin, reduces its activity to inhibit differentiation and maturation of osteoclasts if treated for 10 minutes at 70 °C or for 30 minutes at 56 °C, and lose its activity to inhibit differentiation and maturation of osteoclasts by the treatment for 10 minutes at 90 °C. The amino acid sequence of the protein OCIF which is described in the present invention is clearly different from any of know factors inhibiting formation of osteoclasts.

The invention includes a method to purify OCIF protein, comprising; (1) culturing human fibroblasts, (2) applying the conditioned medium to a heparin column to obtain the adsorbed fraction, (3) purifying the OCIF protein using a cation-exchange column, (4) purifying the OCIF protein using a heparin affinity column, (5) purifying the OCIF protein using a cibacron blue affinity column, (6) isolating the OCIF protein using reverse-phase column chromatography. Cibacron blue F3GA coupled to a carrier made of synthetic hydrophilic polymers is an example of materials used to prepare Cibacron blue columns. These columns are conventionally called "blue colomns".

The invention includes a method for accumulating the OCIF protein to a high concentration by culturing human fibroblasts using alumina ceramic pieces as the cell-adherence matrices.

Moreover, the inventors determined the amino acid sequences of the peptides derived from OCIF, designed the primers based on these amino acid sequences, and obtained cDNA fragments encoding OCIF from a cDNA library of IMR-90 cells.

20 Detailed description of the invention

The OCIF protein of the present invention can be isolated from human fibroblast conditioned medium with high yield. The procedure to isolate OCIF is based on ordinary techniques for purifying proteins from biomaterials, in accordance with the physical and chemical properties of OCIF protein. For example, concentrating procedure includes ordinary biochemical techniques such as ultrafiltration, lyophylization, and dialysis. Purifying procedure includes combinations of several chromatographic techniques for purifying proteins such as ion-exchange column chromatography, affinity column chromatography, gel filtration column chromatography, hydrophobic column chromatography, reverse phase column chromatography, and preparative gel electrophoresis. The human fibroblast used for production of the OCIF protein is preferably IMR-90. A method for producing the IMR-90 conditioned medium is preferably a process comprising, adhering human embryonic fibroblast IMR-90 cells to alumina ceramic pieces in roller-bottles, using DMEM medium supplemented with 5 % new born calf serum for the cell culture, and cultivating the cells in roller-bottles for 7 to 10 days by stand cultivation. CHAPS (3-[(3-cholamid opropyl)-dimethylammonio]-1-propanesulfonate) is prefarably added to the buffer as a detergent in the purification steps of OCIF protein.

OCIF protein of the instant invention can be initially obtained as a heparin binding basic OCIF fraction by applying the culture medium to a heparin column (Heparin-Sepharose CL-6B, Pharmacia), eluting with 10 mM Tris-HCl buffer, pH 7.5, containing 2 M NaCl, and then by applying the OCIF fraction to a Q • anion-exchange column (HiLoad-Q/FF, Pharmacia), and collecting non-adsorbed fraction. OCIF protein can be purified by subjecting the obtained OCIF fraction to purification on a S • cation-exchange column (HiLoad-S/FF, Pharmacia), a heparin column (Heparin-5PW, TOSOH), Cibacrone Blue column (Blue-5PW, TOSOH), and a reverse-phase column (BU-300 C4, Perkin Elmer) and the material is defined by the previously described properties.

The present invention relates to a method of cloning cDNA encoding the OCIF protein based on the amino acid sequence of natural OCIF and a method of obtaining recombinant OCIF protein that inhibits differentiation and/or maturation of osteodasts. The OCIF protein is purified according to the method described in the present invention and is treated with endopeptidase (for example, lysylendopeptidase). The amino acid sequences of the peptides produced by the digestion are determined and the mixture of oligonucleotides that can encode each internal amino acid sequence was systhesized. The OCIF cDNA fragment is obtained by PCR (preferably RT-PCR, reverse transcriptase PCR) using the oligonucleotide mixtures described above as primers. The full length OCIF cDNA encoding the OCIF protein is cloned from a cDNA library using the obtained OCIF DNA fragment as a probe. The OCIF cDNA containing the entire coding region is inserted into an expression vector. The recombinant OCIF can be produced by expressing the OCIF cDNA containing the entire coding region in mammalian cells or bacteria.

The present invention relates to the novel proteins OCIF2, OCIF3, OCIF4, and OCIF5 that are variants of OCIF and have the activity described above. These OCIF variants are obtained from the cDNA library constructed with IMR-90 poly(A) + RNA by hybridization using the OCIF cDNA fragment as a probe. Each of the OCIF variant cDNAs containing the entire coding region is inserted into an expression vector. Each recombinant OCIF variant can be produced by expressing each of the OCIF variant cDNAs containing the entire coding region in the conventional hosts. Each recombinant OCIF variant can be purified according to the method described in this invention. Each recombinant OCIF variant has an ability to inhibit osteoclastogenesis.

The present invention further includes OCIF mutants. They are substitution mutants comprising replacement of one

lane 15; molecular weight marker proteins

lane 16; a monomer type nOCIF protein

lane 17; a dimer type nOCIF protein

lane 18; a monomer type rOCIF(E) protein

lane 19; a dimer type rOCIF(E) protein

lane 20; a monomer type rOCIF(C) protein

lane 21; a dimer type rOCIF(C) protein

Figure 9 shows comparison of amino acid sequences between OCIF and OCIF2.

Figure 10 shows comparison of amino acid sequences between OCIF and OCIF3.

Figure 11 shows comparison of amino acid sequences between OCIF and OCIF4.

Figure 12 shows comparison of amino acid sequences between OCIF and OCIF5.

Figure 13 shows standard curve for determination of OCIF protein concentration by an EIA employing anti-OCIF polyclonal antibodies.

Figure 14 shows standard curve for determination of OCIF protein concentration by an EIA employing anti-OCIF monoclonal antibodies.

Figure 15 shows the effect of rOCIF protein on osteoporosis.

Best Mode for Carrying Out the Invention

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The present invention will be further explained by the following examples, however, the scope of the invention is not restricted to the examples.

EXAMPLE 1

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Preparation of a conditioned medium of human fibroblast IMR-90

Human fetal lung fibroblast IMR-90 (ATCC-CCL186) cells were cultured on alumina ceramic pieces (80 g) (alumina: 99.5%, manufactured by Toshiba Ceramic K.K.) in DMEM medium (manufactured by Gibco BRL Co.) supplemented with 5% CS and 10mM HEPES buffer (500 ml/roller bottle) at 37°C under the presence of 5% $\rm CO_2$ for 7 to 10 days using 60 roller bottles (490 cm², 110 x 171mm, manufactured by Coning Co.)in static culture. The conditioned medium was harvested, and a fresh medium was added to the roller bottles. About 30L of IMR-90 conditioned medium per batch culture was obtained. The conditioned medium was designated as sample 1.

35 EXAMPLE 2

Assay method for osteoclast development inhibitory activity

Osteoclast development inhibitory activity was assayed by measuring tartrate-resistant acid phosphatase(TRAP)

activity according to the methods of M. Kumegawa et.al (Protein · Nucleic Acid · Enzyme, vol.34 p999, 1989) and N. Takahashi et.al (Endocrynology, vol.122, p1373, 1988) with modifications. Briefly, bone marrow cells obtained from 17 day-old mouse were suspended in α-MEM (manufactured by GIBCO BRL Co.) containing 10% FBS, 2x10-8M of activated vitamin D₃, and each test sample, and were inoculated to each well of 96-well plate at a cell density of 3x10⁵ cells/0.2 ml/well. The plates were incubated for 7 days at 37°C in humidified 5%CO₂. Cultures were further continued by replacing 0.16 ml of old medium with the same volume of fresh medium on day 3 and day 5 after starting cultivation. On day 7, after washing the plates with phosphate buffered saline, cells were fixed with ethanol/acetone (1:1) for 1 min. at room temperature, and then osteoclast development was tested by determining for phosphatase activity using a kit (Acid Phosphatase, Leucocyte, Catalog No. 387-A, manufactured by Sigma Co.). The decrease of TRAP positive cells was taken as an indication of OCIF activity.

EXAMPLE 3

Purification of OCIF

i) Heparin Sepharose CL-6B column chromatography

The 90L of IMR-90 conditioned medium (sample 1) was filtrated with 0.22 μ membrane filter (hydrophilic Milidisk, 2000 cm², Milipore Co.), and was divided into three portions. Each portion (30 I) was applied to a heparin Sepharose

CL-6B column (5 x 4.1 cm, Pharmacia Co.) equilibrated with 10mM Tris-HCl containing 0.3M NaCl, pH 7.5. After washing the column with 10mM Tris-HCl, pH 7.5 at a flow rate of 500 ml/hr., heparin Sepharose CL-6B adsorbent protein fraction was eluted with 10mM Tris-HCl, pH 7.5, containing 2M NaCl. The fraction was designated as sample 2.

5 ii) HiLoad-Q/FF column chromatography

The heparin Sepharose-adsorbent fraction (sample 2) was dialyzed against 10mM Tris-HCl, pH 7.5, supplemented with CHAPS to a final concentration of 0.1%, incubated at 4 °C overnight, and divided into two portions. Each portion was then applied to an anion-exchange column (HiLoad-Q/FF, 2.6 x 10 cm, Pharmacia Co.) which was equilibrated with 50mM Tris-HCl, 0.1% CHAPS, pH 7.5 to obtain a non-adsorbent fraction (1000 ml). The fraction was designated as sample 3.

iii) HiLoad-S/HP column chromatography

The HiLoad-Q non-adsorbent fraction (sample 3) was applied to a cation-exchange column (HiLoad-S/HP, 2.6 x 10 cm, Pharmacia Co.) which was equilibrated with 50 mM Tris-HCl, 0.1% CHAPS, pH 7.5. After washing the column with 50 mM Tris-HCl, 0.1% CHAPS, pH 7.5, the adsorbed protein was eluted with linear gradient from 0 to 1 M NaCl at a flow rate of 8 ml/min for 100 min. and fractions (12 ml) were collected. Each ten fractions from number 1 to 40 was pooled to form one portion. Each 100 μl of the four portions was tested for OCIF activity. OCIF activity was observed in fractions from 11 to 30 (as shown in Figure 1). The fractions from 21 to 30 which had higher specific activity were collected and was designated as sample 4.

iv) Heparin-5PW affinity column chromatography

One hundred and twenty ml of HiLoad-S fraction from 21 to 30 (sample 4) was diluted with 240 ml of 50 mM Tris-HCl, 0.1% CHAPS, pH 7.5, and applied to heparin-5PW affinity column (0.8 x 7.5 cm, Tosoh Co.) which was equilibrated with 50mM Tris-HCl, 0.1% CHAPS, pH 7.5. After washing the column with 50mM Tris-HCl, 0.1% CHAPS, pH 7.5, the adsorbed protein was eluted with linear gradient from 0 to 2M NaCl at a flow rate of 0.5ml/min for 60 min. and fractions (0.5 ml) were collected. Fifty μ l was removed from each fraction to test for OCIF activity. The active fractions, eluted with 0.7 to 1.3M NaCl was pooled and was designated as sample 5.

v) Blue 5PW affinity column chromatography

Ten ml of sample 5 was diluted with 190 ml of 50mM Tris-HCl, 0.1% CHAPS, pH 7.5 and applied to a blue-5PW affinity column, (0.5x5 cm, Tosoh Co.) which was equilibrated with 50mM Tris-HCl, 0.1% CHAPS, pH 7.5. After washing the column with 50mM Tris-HCl, 0.1% CHAPS, pH7.5, the adsorbed protein was eluted with a 30 ml linear gradient from 0 to 2M NaCl at a flow rate of 0.5 ml/min., and fractions (0.5 ml) were collected. Using 25 μl of each fraction, OCIF activity was evaluated. The fractions number 49 to 70, eluted with 1.0-1.6M NaCl had OCIF activity.

40 vi) Reverse phase column chromatography

The blue 5PW fraction obtained by collecting fractions from 49 to 50 was acidified with 10μ l of 25% TFA and applied to a reverse phase C4 column (BU-300, 2.1x220mm, manufactured by Perkin-Elmer) which was equilibrated with 0.1% of TFA and 25% of acetonitrile. The adsorbed protein was eluted with linear gradient from 25 to 55% acetonitrile at a flow rate of 0.2 ml/min. for 60 min., and each protein peak was collected (Fig.3). One hundred μ l of each peak fraction was tested for OCIF activity, and peak 6 and the peak 7 had OCIF activity. The result was shown in Table 1.

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Table 1

OCIF activity eluted from reverse phase C4 column

Sample Dilution

1/40 1/120 1/360 1/1080

Peak 6 ++ ++ +
Peak 7 ++ + - -

[++ means OCIF activity inhibiting osteoclast development more than 80%, + means OCIF activity inhibiting osteoclast development between 30% and 80%, and - means no OCIF activity.]

EXAMPLE 4

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Molecular weight of OCIF protein

The two protein peaks (6 and 7) with OCIF activity were subjected to SDS-polyacrylamide gel electrophoresis under reducing and non-reducing conditions. Briefly, 20µl of each peak fraction was concentrated under vacuum and dissolved in 1.5µl of 10mM Tris-HCl, pH 8, 1mM EDTA, 2.5% SDS, 0.01% bromophenol blue, and incubated at 37°C overnight under non-reducing conditions or under reducing conditions (with 5% of 2-mercaptoethanol). Each 1.0 µl of sample was then analyzed by SDS-polyacrylamide gel electrophoresis with a gradient gel of 10-15% acrylamide (Pharmacia Co.) and an electrophoresis-device (Fast System, Pharmacia Co.). The following molecular weight marker proteins were used to calculate molecular weight: phosphorylase b (94 kD), bovine serum albumin (67 kD), ovalbumin (43 kD), carbonic anhydrase (30 kD), trypsin inhibitor (20.0 kD), and lactalbumin (14.4 kD). After electrophoresis, protein bands were visualized by silver stain using Phast Silver Stain Kit. The results were shown in Fig. 4.

A protein band with an apparent 60 KD was detected in the peak 6 protein under both reducing and non-reducing conditions. A protein band with an apparent 60 KD was detected under reducing conditions and a protein band with an apparent 120 KD was detected under non-reducing conditions in the peak 7 protein. Therefore, the protein of peak 7 was considered to be a homodimer of the protein of peak 6.

EXAMPLE 5

Thermostability of OCIF

Twenty μ l of sample from the blue-5PW fractions 51 and 52 was diluted to 30 μ l with 10 mM phosphate buffered saline, pH 7.2, and incubated for 10 min. at 70°C or 90 °C, or for 30 min. at 56°C. The heat-treated samples were tested for OCIF activity. The results were shown in Table 2.

Table 2

		NC Z	
	Thermostat	oility of OCIF	
Sample		Dilution	
	1/300	1/900	1/2700
untreated	++	+	-
70°C, 10 min	+	[- [-
56°C, 30 min	+		-
90°C, 10 min	-		•
		<u></u>	

[++ means OCIF activity inhibiting osteoclast development more than 80%, +means OCIF activity inhibiting osteoclast development between 30% and 80%, and - means no OCIF activity.]

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EXAMPLE 6

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Internal amino acid sequence of OCIF protein

Each 2 fractions (1 ml) from No. 51-70 of blue-5PW fraction was acidified with 10 µl of 25% TFA, and was applied to a reverse phase C4 column (BU-300, 2.1x220mm, manufactured by Perkin-Elmer Co.) equilibrated with 25% of acetonitrile containing 0.1 % TFA. The adsorbed protein was eluted with a 12 ml linear gradient of 25 to 55% acetonitrile at a flow rate of 0.2 ml/min, and the protein fractions corresponding to peak 6 and peak 7 were collected, respectively. The protein of each peak was applied to a protein sequencer (PROCISE 494, Perkin-Elmer Co.). However, the N-terminal sequence of the protein of each peak could not be analyzed. Therefore, N-terminal of the protein of each peak was considered to be blocked. So, internal amino acid sequences of these proteins were analyzed.

The protein of peak 6 or peak 7 purified by C4-HPLC was concentrated by centrifugation and pyridilethylated under reducing conditions. Briefly, 50 μl of 0.5 M Tris-HCl, pH 8.5, containing 100μg of dithiothreitol, 10mM EDTA, 7 M guanidine-HCl, and 1% CHAPS was added to each samples, and the mixture was incubated overnight in the dark at a room temperature. Each the mixture was acidified with 25% TFA (a final concentration 0.1%) and was applied to a reversed phase C4 column (BU-300, 2.1x30mm, Perkin-Elmer Co.) equilibrated with 20 % acetonitrile containing 0.1 % TFA. The pyridil-ethylated OCIF protein was eluted with a 9 ml linear gradient from 20 to 50% acetonitrile at a flow rate of 0.3 ml/min, and each protein peak was collected. The pyridil-ethyrated OCIF protein was concentrated under vacuum, and dissolved in 25μl of 0.1 M Tris-HCl, pH 9, containing 8 M Urea, and 0.1 % Tween 80. Seventy three μl of 0.1 M Tris-HCl, pH 9, and 0.02 μg of lysyl endopeptidase (Wako Pure Chemical, Japan) were added to the tube, and incubated at 37 °C for 15 hours. Each digest was acidified with 1 μl of 25% TFA and was applied to a reverse phase C8 column (RP-300, 2.1x220mm, Perkin-Elmer Co.) equilibrated with 0.1% TFA.

The peptide fragments were eluted from the column with linear gradient from 0 to 50 % acetonitrile at a flow rate of 0.2 ml/min for 70 min., and each peptide peak was collected. Each peptide fragment (P1 - P3) was applied to the protein sequencer. The sequences of the peptides were shown in Sequence Numbers 1 - 3, respectively.

EXAMPLE 7

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Determination of nucleotide sequence of the OCIF cDNA

i) Isolation of poly(A) + RNA from IMR-90 cells

About 10 ug of poly(A) + RNA was isolated from 1x10⁸ cells of IMR-90 by using Fast Track mRNA isolation kit (Invitrogen) according to the manufacturer's instructions.

ii) Preparation of mixed primers

The following two mixed primers were synthesized based on the amino acid sequences of two peptides (peptide P2 and peptide P3, sequence numbers 2 and 3, respectively). All the oligonucleotides in the mixed primers No. 2F can code for the amino acid sequence from the sixth residue, glutamine (Gln) to the twelfth residue, leucine (Leu), in peptide P2. All the oligonucleotides in the mixed primers No. 3R can code for the amino acid sequence from the sixth residue, histidine (His), to the twelfth residue, lysine (Lys), in peptide P3. The sequences of the mixed primers No. 2F and No. 3R were shown in Table 3.

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Table 3

No. 2F

5' -CAAGAACAAA CTTTTCAATT-3'

G G C C GC

A

G

No. 3R

5'-TTTATACATT GTAAAAGAAT G-3'

C G G GCTG

A C

G T

iii) Amplification of OCIF cDNA fragment by PCR (Polymerase chain reaction)

First strand cDNA was generated using Superscript II cDNA synthesis kit (Gibco BRL) and 1 ug of poly (A) + RNA obtained in the example 7-i) according to the manufacturer's instructions. The DNA fragment encoding OCIF was obtained by PCR using the cDNA template and the primers shown in EXAMPLE 7-ii).

40 PCR was performed with the conditions as follows;

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10X Ex Taq Buffer (Takara Shuzo)	5 ul
2.5 mM solution of dNTPs	4 ul
cDNA solution	1 ul
Ex Taq (Takara Shuzo)	0.25 ul
sterile distilled water	29.75 ul
40 uM solution of primers No. 2F	5 ul
40 uM solution of primers No. 3R	5 ul

The components of the reaction were mixed in a microcentrifuge tube. An initial denaturation step at 95 °C for 3 min was followed by 30 cycles of denaturation at 95°C for 30 sec annealing at 50 °C for 30 sec and extention at 70 °C for 2 min. After the amplification, final extention step was performed at 70 °C for 5 min. The size of PCR products were determined on a 1.5 % agarose gel electrophoresis. About 400 bp OCIF DNA fragment was obtained.

EXAMPLE 8

Cloning of the OCIF cDNA fragment amplified by PCR and determination of its DNA sequence

The OCIF cDNA fragment amplified by PCR in EXAMPLE 7-iii) was inserted in the plasmid, pBluescript II SK using DNA ligation kit ver. 2 (Takara Shuzo) according to the method by Marchuk, D. et al. (Nucleic Acids Res., vol 19, p1154, 1991). E.coli. DH5 α (Gibco BRL) was transformed with ligation mixture. The transformants were grown and a plasmid containing the OCIF cDNA (about 400 bp) was purified using the commonly used method. This plasmid was called pBSOCIF. The sequence of OCIF cDNA in pBSOCIF was determined using Taq Dye Deoxy Terminater Cycle Sequencing kit (Perkin Elmer). The size of the OCIF cDNA is 397 bp. The OCIF cDNA encodes an amino acid sequence containing 132 residues. The amino acid sequences of the internal peptides (peptide P2 and peptide P3, sequence number 2 and 3, respectively) that were used to design the primers were found at N- or C- terminal side in the amino acid sequence of the 132 amino acid polypeptide predicted by the 397 bp OCIF cDNA. In addition, the amino acid sequence of the internal peptide P1 (sequence number 1) was also found in the predicted amino acid sequence of the polypeptide. These data show that the 397 bp OCIF cDNA is a portion of the full length OCIF cDNA.

EXAMPLE 9

Preparation of the DNA probe

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The 397 bp OCIF cDNA was prepared according to the conditions described in EXAMPLE 7-iii). The OCIF cDNA was subjected to a preparative agarose gel electrophoresis. The OCIF cDNA was purified from the gel using QIAEX gel extraction kit (QIAGEN), labeled with $[\alpha^{32}P]dCTP$ using Megaprime DNA labeling system (Amersham) and used to select a phage containing the full length OCIF cDNA.

EXAMPLE 10

Preparation of the cDNA library

cDNA was generated using Great Lengths cDNA synthesis kit (Clontech), oligo (dT) primer, [α³²P]dCTP and 2.5 ug of poly(A) + RNA obtained in the example 7-i) according to the manufacturer's instructions. EcoRI-SalI-NotI adaptor was ligated to the cDNA. The cDNA was separated from the free adaptor and unincorporated free [α³²P]dCTP. The purified cDNA was precipitated with ethanol and dissolved in 10 ul of TE buffer (10 mMTris-HCl (pH8.0), 1 mM EDTA). The cDNA with the adaptor was inserted in λZAP EXPRESS vector (Stratagene) at EcoRI site. The recombinant λZAP EXPRESS phage DNA containing the cDNA was in vitro packaged using Gigapack gold II packaging extract (Stratagene) and recombinant λZAP EXPRESS phage library was prepared.

EXAMPLE 11

40 Screening of recombinant phage

Recombinant phages obtained in EXAMPLE 10 were infected to E. Coli, XL1-Blue MRF' (Stratagene) at 37 °C for 15 min.. The infected E.coli cells were added to NZY medium containing 0.7 % agar at 50°C and plated on the NZY agar plates. After the plates were incubated at 37 °C overnight, Hybond N (Amersham) were placed on the surface of plates containing plaques. The membranes were denatured in the alkali solution, neutralized, and washed in 2xSSC according to the standard protocol. The phage DNA was immobilized on the membranes using UV Crosslink (Stratagene). The membranes were incubated in the hybridization buffer (Amersham) containing 100 μg/ml salmon sperm DNA at 65°C for 4 hours and then incubated at 65 °C overnight in the same buffer containing 2x10⁵ cpm/ml denatured OCIF DNA probe. The membranes were washed twice with 2xSSC and twice with a solution containing 0.1xSSC and 0.1 % SDS at 65 °C for 10 min each time. The positive clones were purified by repeating the screening twice. The purified λZAP EXPRESS phage clone containing about 1.6 kb DNA insert was used in the experiments described below. This phage was called λ OCIF. The purified λ OCIF and the infected into E. Coli XL1-Blue MRF (Stratagene) according to a protocol of AZAP EXPRESS cloning kit (Stratagene). The culture broth of infected XL1-Blue MRF was prepared. Purified 1OCIF and ExAssist helper phage (Stratagene) were co-infected into E. coli strain XL-1 blue MRF' according to the protocol supplied with the kit. The culture broth of the co-infected XL-1 blue MRF was added to a culture of E. coli strain XLOR (Stratagene) to transform them. Thus we obtained a Kanamycin-resistant transformant harboring a plasmid designated pBKOCIF which is a pBKCMV (Stratagene) vector containing the 1.6 kb insert fragment. The transformant including the plasmid containing about 1.6 kb OCIF cDNA was obtained by picking up the kanamycin-

resistant colonies. The plasmid was called pBKOCIF. The transformant has been deposited to National Institute of Bioscience and Human-Technology (NIBH), Agency of Industrial Science and Tecnology as "FERM BP-5267" as pBK/O1F10. A national deposit (Accession number, FERM P-14998) was transferred to the international deposit, on October 25, 1995 according to the Budapest treaty. The transformant pBK/O1F10 was grown and the plasmid pBKOCIF was purified according to the standard protocol.

EXAMPLE 12

Determination of the nucleotide sequence of OCIF cDNA containing the full coding region.

The nucleotide sequence of OCIF cDNA obtained in EXAMPLE 11 was determined using Taq Dye Deoxy Terminater Cycle Sequencing kit (Perkin Elmer). The primers used were T3, T7 primers (Stratagene) and synthetic primers designed according to the OCIF cDNA sequence. The sequences of these primers are shown in sequence numbers 16 to 29. The nucleotide sequence of the OCIF cDNA is shown in sequence number 6 and the amino acid sequence predicted by the cDNA sequence is shown in sequence number 5.

EXAMPLE 13

Production of recombinant OCIF by 293/EBNA cells

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i) Construction of the plasmid for expressing OCIF cDNA

pBKOCIF containing about 1.6 kb OCIF cDNA was prepared as described in EXAMPLE 11, and digested with restriction enzymes, BamHl and Xhol. The OCIF cDNA insert was cut out, separated by an agarose gel electrophoresis, and purified using QIAEX gel extraction kit (QIAGEN). The purified OCIF cDNA insert was ligated using DNA ligation kit ver. 2 (Takara Shuzo) to the expression vector pCEP4 (Invitrogen) digested with restriction enzymes, BamHl and Xhol. E.coli. DH5α (Gibco BRL) was transformed with the ligation mixture. The transformants were grown and the plasmid containing the OCIF cDNA (about 1.6 kb) was purified using QIAGEN column (QIAGEN). The expression plasmid pCEPOCIF was precipitated with ethanol, and dissolved in sterile distilled water was used in the expreriments described below.

ii) Transient expression of OCIF cDNA and analysis of the biological activity

Recombinant OCIF was produced using the expression plasmid, pCEPOCIF prepared in EXAMPLE 13-i) according to the method described below. 8x10⁵ cells of 293/EBNA (Invitrogen) were inoculated in each well of the 6-well plate using IMDM containing 10 % fetal calf serum (Gibco BRL). After the cells were incubated for 24 hours, the culture medium was removed and the cells were washed with serum free IMDM. The expression plasmid, pCEPOCIF and lipofectamine (Gibco BRL) were diluted with OPTI-MEM (Gibco BRL) and were mixed, and added to the cells in each well according to the manufacture's instructions. Three μg of pCEPOCIF and 12 μl of lipofectamine were used for each transfection. After the cells were incubated with pCEPOCIF and lipofectamine for 38 hours, the medium was replaced with 1 ml of OPTI-MEM. After the transfected cells were incubated for 30 hours, the conditioned medium was harvested and used for the biological assay. The biological activity of OCIF was analysed according to the method described below. Bone marrow cells obtained from mice, 17 days-old, were suspended in α -MEM (manufactured by GIBCO BRL Co.) containing 10% FBS, 2x10⁻⁸M activated vitamin D₃, and each test sample, and were inoculate and cultured for 7 days at 37°C in humidified 5%CO2 as described in EXAMPLE 2. During incubation, 160 µl of old medium in each well was replaced with the same volume of the fresh medium containing test sample diluted with 1x10⁻⁸M of activated vitamin D_3 and α -MEM containing FBS on day 3 and day 5. On day 7, after washing the wells with phosphate buffered saline, cells were fixed with ethanol/acetone (1:1) for 1 min. and then osteoclast development was tested using acid phosphatase activity mesuring kit (Acid Phosphatase, Leucocyte, Catalog No. 387-A, Sigma Co.). The decrease of the number of TRAP positive cells was taken as an OCIF activity. As result, the conditioned medium showed the same OCIF activity as natural OCIF protein from IMR-90 conditioned medium (Table 4).

Table 4

Cultured Cell	Dilution							
	1/20	1/40	1/80	1/160	1/320	1/640	1/1280	
OCIF expression vector transfected	++	++	++	++	++	+		
vector transfected	-	•	-	-	•	-		
untreated	-	-	•	-	-	-	 -	

iii) Isolation of recombinant OCIF protein from 293/EBNA-conditioned medium

293/EBNA-conditioned medium (1.8 I) obtained by cultivating the cells described in example 13-ii) was supplemented with 0.1 % of CHAPS and filtrated with 0.22 μm membrane filter (Steribecs GS, Milipore Co.). The conditioned medium was applied to 50 ml of a heparin Sepharose CL-6B column (2.6 x 10 cm, Pharmacia Co.) equilibrated with 10mM Tris-HCl, pH 7.5. After washing the column with 10mM Tris-HCl, pH 7.5, the adsorbed protein was eluted from the column with linear gradient from 0 to 2 M NaCl at a flow rate of 4 ml/min for 100 min. and fractions (8 ml) were collected. Using 150 μl of each fraction, OCIF activity was assayed according to the method described in EXAMPLE 2. OCIF active fraction (112 ml) eluted with approximately 0.6 to 1.2 M NaCl was obtained.

One hundred twelve ml of the active fraction was diluted to 1000 ml with 10 mM Tris-HCl, 0.1% CHAPS, pH 7.5, and applied to a heparin affinity column (heparin-5PW, 0.8 x 7.5 cm, Tosoh Co.) equilibrated with 10mM Tris-HCl, 0.1% CHAPS, pH 7.5. After washing the column with 10mM Tris-HCl, 0.1% CHAPS, pH 7.5, the adsorbed protein was eluted from the column with linear gradient from 0 to 2 M NaCl at a flow rate of 0.5ml/min for 60 min., and fractions (0.5 ml) were collected. Four µl of each fraction was analyzed by SDS-polyacrylamide gel electrophoresis under reducing and non-reducing conditions as described in EXAMPLE 4. On SDS-PAGE under reducing conditions, a single band of rOCIF protein with an apparent 60 KD was detected in fractions from 30 to 32, under non-reducing conditions, bands of rOCIF protein with an apparent 60 KD and 120 KD were also detected in fractions from 30 to 32. The isolated rOCIF fraction from 30 to 32 was designated as recombinant OCIF derived from 293/EBNA (rOCIF(E)). 1.5 ml of the rOCIF(E) (535 µg/ml) was obtained when determined by the method of Lowry using bovine serum albumin as a standard protein.

EXAMPLE 14

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Production of recombinant OCIF using CHO cells

i) Construction of the plasmid for expressing OCIF

pBKOCIF containing about 1.6 kb OCIF cDNA was prepared as described in EXAMPLE 11, and digested with restriction enzymes, Sall and EcoRV. About 1.4 kb OCIF cDNA insert was separated by an agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The expression vector, pcDL-SR α296 (Molecular and Cellular Biology, vol 8, p466, 1988) was digested with restriction enzymes, Pstl and Kpnl. About 3.4 kb of the expression vector fragment was cut out, separated by agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The ends of the purified OCIF cDNA insert and the expression vector fragment were blunted using DNA blunting kit (Takara Shuzo). The purified OCIF cDNA insert and the expression vector fragment were ligated using DNA ligation kit ver. 2 (Takara Shuzo). E.coli. DH5a α (Gibco BRL) was transformed with the ligation mixture. The transformant containing the OCIF expression plasmid, pSRαOCIF was obtained.

ii) Preparation of expression plasmid

The transformant containing the OCIF expression plasmid, pSR αOCIF preprared in the example 13-i) and the transformant containing the mouse DHFR expression plasmid, pBAdDSV shown in WO92/01053 were grown according to the standard method. Both plasmids were purified by alkali treatment, polyethylene glycol precipitation, and cesium chrolide density gradient ultra centrifugation according to method of Maniatis et al. (Molecular cloning, 2nd edition).

iii) Adaptation of CHOdhFr- cells to the protein free medium

CHOdhFr- cells (ATCC, CRL 9096) were cultured in IMDM containing 10 % fetal calf serum. The cells were adapted to EX-CELL 301 (JRH Biosciecnce) and then adapted to EX-CELL PF CHO (JRH Biosciecnce) according to the manufacture's instructions.

iv) Transfection of the OCIF expression plasmid, and the mouse DHFR expression plasmid, to CHOdhFr- cells.

CHOdhFr- cells prepared in EXAMPLE 14-iii) were transfected by electroporation with pSRαOCIF and pBAdDSV prepared in EXAMPLE 14-ii). 200 μg of pSRαOCIF and 20 μg of pBAdDSV were dissolved under sterile conditions in 0.8 ml of IMDM (Gibco BRL) containing 10 % fetal calf serum CG. 2x10⁷ cells of CHOdhFr- were suspended in 0.8 ml of this medium. The cell suspension was transferred to a cuvette (Bio Rad) and the cells were transfected by electroporation using gene pulser (Bio Rad) under condition of 360 V and 960 μF. The suspension of electroporated cells was transferred to T-flasks (Sumitomo Bakelite) containing 10 ml of EX-CELL PF-CHO, and incubated in the CO₂ incubator for 2 days. Then the transfected cells were inoculated in each well of a 96 well plate (Sumitomo Bakelite) at a density of 5000 cells/well and cultured for about 2 weeks. The transformants expressing DHFR are selected since EX-CELL PF-CHO does not contain nucleotides and the parental cell line CHO dhFr- can not grow in this medium. Most of the transformants expressing DHFR express OCIF since the OCIF expression plasmid was used ten times as much as the mouse DHFR expression plasmid. The transformants whose conditioned medium had high OCIF activity were selected among the transformants expressing DHFR according to the method described in EXAMPLE 2. The transformants that express large amounts of OCIF were cloned by limiting dilution. The clones whose conditioned medium had high OCIF activity were selected as described above and the transformant expressing large amount of OCIF, 5561, was obtained.

v) Production of recombinant OCIF

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To produce recombinant OCIF (rOCIF), EX-CELL 301 medium (3 I) in a 3 I-spiner flask was inoculated with the clone (5561) at a cell-density of 1x10⁵ cells/ml. The 5561 cells were cultured in a spiner flask at 37°C for 4 to 5 days. When the concentration of the 5561 cells reached to 1x10⁶ cells/ml, about 2.7 I of the conditioned medium was harvested. Then about 2.7 I of EX-CELL 301 was added to the spiner flask and the 5561 cells were cultured repeatedly. About 20 I of the conditioned medium was harvested using the three spiner flasks.

vi) Isolation of recombinant OCIF protein from CHO cells-conditioned medium

CHOcells-conditioned medium (1.0 l) described in EXAMPL 14-v) was supplemented with 1.0 g of CHAPS and filtrated with 0.22 µm membrane filter (Steribecks GS, Milipore Co.). The conditioned medium was applied to a heparin Sepharose-FF column (2.6 x 10 cm, Pharmacia Co.) equilibrated with 10 mM Tris-HCl, pH 7.5. After washing the column with 10 mM Tris-HCl, 0.1 % CHAPS, pH 7.5, the adsorbed protein was eluted from the column with linear gradient from 0 to 2 M NaCl at a flow rate of 4 ml/min for 100 min. and fractions (8 ml) were collected. Using 150µl of each fraction, OCIF activity was assayed according to the method described in EXAMPLE 2. Active fraction (112 ml) eluted with approximately 0.6 to 1.2 M NaCl was obtained.

The 112 ml of active fraction was diluted to 1200 ml with 10 mM Tris-HCl, 0.1% CHAPS, pH 7.5, and applied to a affinity column (blue-5PW, 0.5 x 5.0 cm, Tosoh Co.) equilibrated with 10 mM Tris-HCl, 0.1% CHAPS, pH 7.5. After washing the column with 10 mM Tris-HCl, 0.1% CHAPS, pH 7.5, the adsorbed protein was eluted from the column with linear gradient from 0 to 3 M NaCl at a flow rate of 0.5ml/min for 60 min., and fractions (0.5 ml) were collected. Four µl of each fraction was subjected to SDS-polyacrylamide gel electrophoresis under reducing and non-reducing conditions as described in EXAMPLE 4. On SDS-PAGE under reducing conditions, a single band of rOCIF protein with apparent 60 KD was detected in fractions 30 to 38, under non-reducing conditions, bands of rOCIF protein with apparent 60 KD and 120 KD were also detected in fractions 30 to 38. The isolated rOCIF fraction, 30 to 38, was designated as purified recombinant OCIF derived from CHO cells (rOCIF(C)). 4.5 ml of the rOCIF(C) (113 µg/ml) was obtained when determined by the method of Lowry using bovine serum albumin as a standard protein.

EXAMPLE 15

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Determination of N-terminal amino acid sequence of rOCIFs

Each 3 µg of the isolated rOCIF(E) and rOCIF(C) was adsorbed to polyvinylidene difluoride (PVDF) membranes with Prospin (PERKIN ELMER Co.). The membranes were washed with 20 % ethanol and the N-terminal amino acid sequences of the adsorbed proteins were analyzed by protein sequencer (PROCISE 492, PERKIN ELMER Co.). The

determined N-terminal amino acid sequence is shown in sequence No. 7.

The N-terminal amino acid of rOCIF(E) and rOCIF(C) was the 22th amino acid of glutamine from Met as translation starting point, as shown in sequence number 5. The 21 amino acids from Met to Gln were identified as a signal peptide. The N-terminal amino acid sequence of OCIF isolated from IMR-90 conditioned medium was undetectable. Accordingly, the N-terminal glutamine of OCIF may be blocked by converting from glutamine to pyroglutamine within culturing or purifing.

EXAMPLE 16

- 10 Biological activity of recombinant(r) OCIF and natural(n) OCIF
 - i) Inhibition of vitamin D₃ induced osteodast formation from murine bone marrow cells

Each the rOCIF(E) and nOCIF sample was diluted with α -MEM (GIBCO BRL Co.) containing 10% FBS and 2x10-8M of activated vitamin D_3 (a final concentration of 250 ng/ml). Each sample was serially diluted with the same medium, and 100 μ l of each diluted sample was added to each well in 96-well plates. Bone marrow cells obtained from mice, 17 days-old, were inoculated at a cell density of $3x10^5$ cells/ 100μ l/ well to each well in 96-well plates and cultured for 7 days at 37°C in humidified $5\%\text{CO}_2$. On day 7, the cells were fixed and stained with a acid phosphatase mesuring kit (Acid Phosphatase, Leucocyte, No387-A, Sigma) according to the method described in EXAMPLE 2. The decrease of acid phosphatase activity (TRAP) was taken as OCIF activity. The decrease of acid phosphatase-positive cells was evaluated by solubilizing the pigment of dye and measuring absorbance. In detail, 100 μ l of a mixture of 0.1 N NaOH and dimethylsulfoxide (1:1) was added to each well and the well was vibrated to solubilize the dye. After solubilizing the dye completely, an absorbance of each well was measured at 590 nm subtracting the absorbance at 490 nm using microplate reader (Immunoreader NJ-2000, InterMed). The microplate reader was adjusted to 0 absorbance using a well with monolayered bone marrow cells which was cultured in the medium without activated vitamin D_3 . The decrease of TRAP activity was expressed as a percentage of the control absorbance value (=100%) of the solubilized dye from wells with bone marrow cells which were cultured in the absence of OCIF. The results are shown in Table 5.

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Table 5

Inhibition of vitamin D3-induced osteoclast formation from murine bone marrow cells							
OCIF concentra- tion(ng/ml)	250	125	63	31	16	0	
rOCIF(E)	0	0	3	62	80	100	
nOCIF .	0	0	27	27	75	100 (%)	

Both nOCIF and rOCIF(E) inhibited osteoclast formation in a dose dependent manner in the concentration of 16 ng/ml or higher

- ii) Inhibition of vitamin D3-induced osteoclast formation in co-cultures of stromal cells and mouse spleen cells.
- Effect of OCIF on osteoclast formation induced by Vitamin D₃ in co-cultures of stromal cells and mouse spleen cells was tested according to the method of N. Udagawa et al. (Endocrinology, vol. 125, p1805-1813, 1989). In detail, each of rOCIF(E), rOCIF(C), and nOCIF sample was serially diluted with α-MEM (GIBCO BRL Co.) containing 10% FBS, 2x10⁻⁸M of activated vitamin D₃, and 2x10⁻⁷M dexamethasone, and 100μl of each the diluted samples was added to each well in 96 well-microwell plates. Murine bone marrow-derived stromal ST2 cells (RIKEN Cell Bank RCB0224); 5x10³ cells per 100μl of α-MEM containing 10% FBS, and spleen cells from ddy mice, 8 weeks-old, ; 1x10⁵ cells per 100 μl in the same medium, were inoculated to each well in 96-well plates and cultured for 5 days at 37°C in humidified 5%CO₂. On day 5, the cells were fixed and stained with a kit for acid phosphatase (Acid Phosphatase, Leucocyte, No387-A, Sigma). The decrease of acid phosphatase-positive cells was taken as OCIF activity. The decrease of acid phosphatase-positive cells was evaluated according to the method described in EXAMPLE 16-i). The results are shown in Table 6; rOCIF(E) and rOCIF(C), and Table 7; rOCIF(E) and nOCIF.

Table 6

Inhibition of osteoclast formation in co-cultures of stromal cells and mouse spleen cells.						
OCIF concentra- tion(ng/ml)	50	25	13	6	0	
rOCIF(E)	3	22	83	80	100	
rOCIF(C)	13	19	70	96	100 (%)	

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Table 7

Inhibition of osteoclast fo	rmation in co spleen		stromal cell	s and mouse
OCIF concentra- tion(ng/ml)	250	63	16	0
rOCIF(E)	7	27	37	100
rOCIF(C)	13	23	40	100 (%)
nOCIF, rOCIF(E) and rO dependent manner in the	CIF(C) inhib	ited osteocla	ast formations/ml or high	on in a dose er

iii) Inhibition of PTH-induced osteoclast formation from murine bone marrow cells.

Effect of OCIF on osteoclast formation induced by PTH was tested according to the method of N. Takahashi et al. (Endocrinology, vol. 122, p1373-1382, 1988). In detail, each the rOCIF(E) and nOCIF sample (125 ng/ml) was serially diluted with α -MEM (manufactured by GIBCO BRL Co.) containing 10% FBS and 2x10⁻⁸M PTH, and 100 μ l of each the diluted samples was added to 96 well-plates. Bone marrow cells from ddy mice, 17 days-old, at a cell density of 3x10⁵ cells per $100\mu l$ of α -MEM containing 10% FBS were inoculated to each well in 96-wells plates and cultured for 5 days at 37°C in humidified 5%CO2. On day 5, the cells were fixed with ethanol/aceton (1:1) for 1 min. at room temperature and stained with a kit for acid phosphatase (Acid Phosphatase, Leucocyte, No387-A, Sigma) according to the method described in EXAMPLE 2. The decrease of acid phosphatase-positive cells was taken as OCIF activity. The decrease of acid phosphatase-positive cells was evaluated according to the method described in EXAMPLE 16-i). The results are shown in Table 8.

Table 8

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0

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100

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Inhibition of PTH-induced osteoclast formation from murine bone marrow cells. OCIF concentra-125 63 31 16 tion(ng/ml) rOCIF(E) 6 58 58 53 88 nOCIF 18 47 53 56

nOCIF and rOCIF(E) inhibited osteoclast formation in a dose dependent manner in the concentration of 16 ng/ml or higher

iv) Inhibition of IL-11-induced osteoclast formation

Effect of OCIF on osteoclast formation induced by IL-11 was tested according to the method of T. Tamura et al. (Proc. Natl. Acad. Sci. USA, vol. 90, p11924-11928, 1993). In detail, each rOCIF(E) and nOCIF sample was serially

diluted with α -MEM (GIBCO BRL Co.) containing 10% FBS and 20 ng/ml IL-11 and 100 μ l of each the diluted sample was added to each well in 96-well plates. Newborn mouse calvaria-derived pre-adipocyte MC3T3-G2/PA6 cells (RIKEN Cell Bank RCB1127); $5x10^3$ cells per 100μ l of α -MEM containing 10% FBS, and spleen cells from ddy mouse, 8 weeks-old,; $1x10^5$ cells per 100μ l in the same medium, were inoculated to each well in 96-well plates and cultured for 5 days at 37 °C in humidified 5%CO2. On day 5, the cells were fixed and stained with a kit for acid phosphatase (Acid Phosphatase, Leucocyte, No387-A, Sigma). Acid phosphatase positive cells were counted under microscope and a decrease of the cell numbers was taken as OCIF activity. The results are shown in Table 9.

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Table 9

OCIF concentra- tion(ng/ml)	500	125	31	7.8	2.0	0.5	0
nOCIF	0	0	1	4	13	49	31
rOCIF(E)	0	0	1	3	10	37	31

Both nOCIF and rOCIF(E) inhibited osteoclast formation in a dose dependent manner in the concentration of 2 ng/ml or higher

The results shown in Table 4-8 indicated that OCIF inhibits all the vitamin D₃, PTH, and IL-11-induced osteoclast formations at almost the same doses. Accordingly, OCIF would be able to be used for treatment of the different types of bone disorders with decreased bone mass, which are caused by different substances which induce bone resorption.

EXAMPLE 17

Isolation of monomer-type OCIF and dimer-type OCIF

Each rOCIF(E) and rOCIF(C) sample containing 100 µg of OCIF protein, was supplemented with 1/100 volume of 25 % trifluoro acetic acid and applied to a reverse phase column (PROTEIN-RP, 2.0x250 mm, YMC Co.) equilibrated with 30 % acetonitrile containing 0.1 % trifluoro acetic acid. OCIF protein was eluted from the column with linear gradient from 30 to 55 % acetonitrile at a flow rate of 0.2 ml/min for 50 min. and each OCIF peak was collected. Each the monomer-type OCIF peak fraction and dimer-type OCIF peak fraction was lyophilized, respectively.

EXAMPLE 18

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Determination of molecular weight of recombinant OCIFs

Each 1 µg of the isolated monomer-type and dimer-type nOCIF purified using reverse phase column according to EXAMPLE 3-iv) and each 1 µg of monomer-type and dimer-type rOCIF described in EXAMPLE 17 was concentrated under vaccum, respectively. Each sample was incubated in the buffer for SDS-PAGE, subjected to SDS-polyacrylamide gel electrophoresis, and protein bands on the gel were stained with silver according to the method described in EXAMPLE 4. Results of electrophoresis under non-reducing conditions and reducing conditions are shown in Figure 6 and Figure 7.

A protein band with an apparent molecular weight of 60 KD was detected in each monomer-type OCIF sample, and a protein band with an apparent molecular weight of 120 KD was detected in each dimer-type OCIF sample in non-reducing conditions. A protein band with an apparent molecular weight of 60 KD was detected in each monomer-type OCIF sample under reducing conditions. Accordingly, molecular weights of monomer-type nOCIF from IMR-90 cells, rOCIF from 293/EBNA cells and rOCIF from CHO cells were almost the same. Molecular weights of dimer-type nOCIF from IMR-90 cells, rOCIF from 293/EBNA cells, and rOCIF from CHO cells were also the same.

EXAMPLE 19

Remove N-linked Oligosaccharide chain and Mesuring molecular weight of natural and recombinant OCIF

Each sample containing 5μg of the isolated monomer-type and dimer-type nOCIF purified using reverse phase column according to EXAMPLE 3-iv) and each sample containing 5 μg of monomer-type and dimer-type rOCIF described in EXAMPLE 17 were concentrated under vaccum. Each sample was dissolved in 9.5 μl of 50 mM sodium phosphate buffer, pH 8.6, containing 100 mM 2-mercaptoethanol, supplemented with 0.5 μl of 250 U/ml N-glycanase (Seikagaku

kogyo Co.) and incubated for one day at 37 °C. Each sample was supplemented with 10 μ l of 20 mM Tris-HCl, pH 8.0 containing 2 mM EDTA, 5 % SDS, and 0.02 % bromo-phenol blue and heated for 5 min at 100 °C. Each 1 μ l of the samples was subjected to SDS-polyacrylamide gel electrophoresis, and protein bands on the gel were stained with silver as described in EXAMPLE 4. The patterns of electrophoresis are shown in Figure 8.

An apparent molecular weight of each the deglycosylated nOCIF from IMR-90 cells, rOCIF from CHO cells, and rOCIF from 293/EBNA cells was 40 KD under reducing conditions. An apparent molecular weight of each untreated nOCIF from IMR-90 cells, rOCIF from 293/EBNA cells, and rOCIF from CHO cells was 60 KD under reducing conditions. Accordingly, the results indicate that the OCIF proteins are glycoproteins with N-linked sugar chains.

O EXAMPLE 20

Cloning of OCIF variant cDNAs and determination of their DNA squences

The plasmid pBKOCIF, which is inserted OCIF cDNA to pBKCMV (Stratagene), was obtained from one of some purified positive phage as in example 10 and 11. And more, during the screening of the cDNA library with the 397 bp OCIF cDNA probe, the transformants containing plasmids whose insert sizes were different from that of pBKOCIF were obtained. These transformants containing the plasmids were grown and the plasmids were purified according to the standard method. The sequence of the insert DNA in each plasmid was determined using Taq Dye Deoxy Terminater Cycle Sequencing kit (Perkin Elmer). The used primers were T3, T7 primers (Stratagene) and synthetic primers prepared based on the nucleotide sequence of OCIF cDNA. There are four OCIF variants (OCIF2, 3, 4, and 5) in addition to OCIF. The nucleotide sequence of OCIF2 is shown in the sequence number 8 and the amino acid sequence of OCIF3 is shown in the sequence number 10 and the amino acid sequence of OCIF3 predicted by the nucleotide sequence is shown in the sequence number 11. The nucleotide sequence of OCIF4 is shown in the sequence number 12 and the amino acid sequence of OCIF5 predicted by the nucleotide sequence is shown in the sequence number 13. The nucleotide sequence of OCIF5 is shown in the sequence number 14 and the amino acid sequence of OCIF5 predicted by the nucleotide sequence is shown in the sequence is shown in the sequence number 15. The structures of OCIF variants are shown in Figures 9 to 12 and are described in brief below. OCIF2

OCIF2 cDNA has a deletion of 21 bp from guanine at nucleotide number 265 to guanine at nucleotide number 285 in OCIF cDNA (sequence number 6). Accordingly OCIF2 has a deletion of 7 amino acids from glutamic acid (Glu) at amino acid number 68 to glutamine (Gln) at amino acid number 74 in OCIF (sequence number 5).

OCIF3

OCIF3 cDNA has a point mutation at nucleotide number 9 in OCIF cDNA (sequence number 6) where cytidine is replaced with guanine.

Accordingly OCIF3 has a mutation and asparagine (Asn) at amino acid number -19 in OCIF (sequence number 5) is replaced with lysine (Lys). The mutation seems to be located in the signal sequence and have no essential effect on the secreted OCIF3. OCIF3 cDNA has a deletion of 117 bp from guanine at nucleotide number 872 to cytidine at nucleotide number 988 in OCIF cDNA (sequence number 6).

Accordingly OCIF3 has a deletion of 39 amino acids from threonine (Thr) at amino acid number 270 to leucine (Leu) at amino acid number 308 in OCIF (sequence number 5).

OCIF4

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OCIF4 cDNA has two point mutations in OCIF cDNA (sequence number 6). Cytidine at nucleotide number 9 is replaced with guanine and guanine at nucleotide number 22 is replaced with thymidine in OCIF cDNA (sequence number 6).

Accordingly OCIF4 has two mutations. Asparagine (Asn) at amino acid number -19 in OCIF (sequence number 5) is replaced with lysine (Lys), and alanine (Ala) at amino acid number -14 is replaced with serine (Ser). These mutations seem to be located in the signal sequence and have no essential effect on the secreted OCIF4. OCIF4 cDNA has about 4 kb DNA, which is the intron 2 of OCIF gene, inserted between nucleotide number 400 and

nucleotide number 401 in OCIF cDNA (sequence number 6). The open reading frame stops in intron 2. Accordingly OCIF4 has an additional novel amino acid sequence containing 21 amino acids after alanine (Ala) at amino acid number 112 in OCIF (sequence number 5).

OCIF5

OCIF5 cDNA has a point mutation at nucleotide number 9 in OCIF cDNA (sequence number 6) where cytidine is replaced with guanine.

- Accordingly OCIF5 has a mutation and asparagine (Asn) at amino acid number -19 in OCIF (sequence number 5) is replaced with lysine (Lys). The mutation seems to be located in the signal sequence and have no essential effect on the secreted OCIF5.
 - OCIF5 cDNA has the latter portion (about 1.8 kb) of intron 2 between nucleotide number 400 and nucleotide number 401 in OCIF cDNA (sequence number 6). The open reading frame stops in the latter portion of intron 2.
- Accordingly OCIF5 has an additional novel amino acid sequence containing 12 amino acids after alanine (Ala) at amino acid number 112 in OCIF (sequence number 5).

EXAMPLE 21

- 15 Production of OCIF variants
 - i) Construction of the plasmid for expressing OCIF variants

The plasmid containing OCIF2 or OCIF3 cDNA was obtained as described in EXAMPLE 20 and called pBKOCIF2 and pBKOCIF3, respectively. pBKOCIF2 and pBKOCIF3 were digested with restriction enzymes, BamHI and XhoI. The OCIF2 and OCIF3 cDNA inserts were separated by agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The purified OCIF2 and OCIF3 cDNA inserts were individually ligated using DNA ligation kit ver. 2 (Takara Shuzo) to the expression vector pCEP4 (Invitrogen) that had been digested with restriction enzymes, BamHI and XhoI. E. coli. DH5α (Gibco BRL) was transformed with the ligation mixture.

- The plasmid containing OCIF4 cDNA was obtained as described in EXAMPLE 20 and called pBKOCIF4. pBKOCIF4 was digested with restriction enzymes, Spel and Xhol (Takara Shuzo). The OCIF4 cDNA insert was separated by an agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The purified OCIF4 cDNA insert was ligated using DNA ligation kit ver. 2 (Takara Shuzo) to the expression vector pCEP4 (Invitrogen) that had been digested with restriction enzymes, Nhel and Xhol (Takara Shuzo). E.coli. DH5 α (Gibco BRL) was transformed with the ligation mixture.
 - The plasmid containing OCIF5 cDNA was obtained as described in EXAMPLE 20 and was called pBKOCIF5. pBKOCIF5 was digested with restriction enzyme, HindIII (Takara Shuzo). The 5' portion of the coding region in the OCIF5 cDNA insert was separated by agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The OCIF expression plasmid, pCEPOCIF, obtained in EXAMPLE 13-i) was digested with restriction enzyme, HindIII (Takara Shuzo). The 5' portion of the coding region in the OCIF cDNA was removed. The rest of the plasmid that contains pCEP vector and the 3' portion of the coding region of OCIF cDNA was called pCEPOCIF-3'. pCEPOCIF-3' was separated by an agarose gel electrophoresis, and purified from the gel using QIAEX gel extraction kit (QIAGEN). The OCIF5 cDNA HindIII fragment and pCEPOCIF-3' were ligated using DNA ligation kit ver. 2 (Takara Shuzo). E.coli. DH5 α (Gibco BRL) was transformed with the ligation mixture.
- The obtained transformants were grown at 37 °C overnight and the OCIF variants expression plasmids (pCEPOCIF2, pCEPOCIF3, pCEPOCIF4, and pCEPOCIF5) were purified using QIAGEN column (QIAGEN). These OCIF-variants-expression plasmids were precipitated with ethanol, dissolved in sterile distilled water, and used in the expreriments described below.
- 45 ii) Transient expression of OCIF variant cDNAs and analysis of the biological activity of recombinant OCIF variants.

Recombinant OCIF variants were produced using the expression plasmid, pCEPOCIF2, pCEPOCIF3, pCEPOCIF3, pCEPOCIF4, and pCEPOCIF5 prepared as described in EXAMPLE 21-i) according to the method described in EXAMPLE 13-ii). The biological activities of recombinant OCIF variants were analyzed. The results were that these OCIF variants (OCIF2, OCIF3, OCIF4, and OCIF5) had a weak activity.

EXAMPLE 22

Preparation of OCIF mutants

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i) Construction of a plasmid vector for subdoning cDNAs encoding OCIF mutants

The plasmid vector (5 μ g) described in EXAMPLE 11 was digested with restriction enzymes Bam HI and Xho I (

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Takara Shuzo). The digested DNA was subjected to a preparative agarose gel electrophoresis. DNA fragment with an approximate size of 1.6 kilobase pairs (kb) that contained the entire coding sequence for OCIF was purified from the gel using QIAEX gel extraction kit (QIAGEN). The purified DNA was dissolved in 20 μ I of sterile distilled water. This solution was designated DNA solution 1. p Bluescript II SK + (3 μ g) (Stratagene) was digested with restriction enzymes Bam HI and Xho I (Takara Shuzo). The digested DNA was subjected to preparative agarose gel electrophoresis. DNA fragment with an approximate size of 3.0 kb was purified from the gel using QIAEX DNA extraction kit (QIAGEN). The purified DNA was dissolved in 20 μ I of sterile distilled water. The solution was designated DNA solution 2. One microliter of DNA solution 2, 4 μ I of DNA solution 1 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 (Takara Shuzo) were mixed and incubated at 16 °C for 30 min. (The ligation mixture was used for the transformation of E. coli in a manner described below). Conditions for transformation of E. coli were as follows. One hundred microliters of competent E. coli DH5 α cells (GIBCO BRL) and 5μ I of the ligation mixture was mixed in a sterile 15-ml tube (IWAKI glass). The tube was kept on ice for 30 min. After incubation for 45 sec at 42°C, to the cells was added 250 μ I of L broth (1% Tryptone, 0.5% yeast extract, 1% NaCl). The cell suspension was then incubated for 1hr. at 37°C with shaking. Fifty microliters of the cell suspension was plated onto an L-agar plate containing 50 μ g/ml of ampicillin. The plate was incubated overnight at 37°C.

Six colonies which grew on the plate were individually incubated in 2 ml each of L-broth containing 50µg/ml of ampicillin overnight at 37°C with shaking. The structure of the plasmids in the colonies was analyzed. A plasmid in which the 1.6-kb DNA fragment containing the entire OCIF cDNA is inserted between the digestion sites of Bam HI and Xho I of pBluescript II SK + was obtained and designated as pSK + -OCIF.

- ii) Preparation of mutants in which one of the Cys residues in OCIF is replaced with Ser residue
 - 1) Introduction of mutations into OCIF cDNA

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OCIF mutants were prepared in which one of the five Cys residues present in OCIF at positions 174, 181, 256, 298 and 379 (in SEQUENCE NO 4) was replaced with Ser residue and were designated OCIF-C19S(174Cys to Ser), OCIF-C20S (181Cys to Ser), OCIF-C21S (256Cys to Ser), OCIF-C22S (298Cys to Ser) and OCIF-C23S (379Cys to Ser), respectively.

To prepare the mutants, nucleotides encoding the corresponding Cys residues were replaced with those encoding Ser. Mutagenesis was carried out by a two-step polymerase chain reaction (PCR). The first step of the PCRs consisted of two reactions, PCR 1 and PCR 2.

PCR 1	10X Ex Taq Buffer (Takara Shuzo)	10 µl
	2.5 mM solution of dNTPs	لبر 8
	the plasmid vector described in EXAMPLE 11 (8ng/ml)	2 µ
[sterile distilled water	73.5 µl
l	20 μM solution of primer 1	5 µl
	100 μM solution of primer 2 (for mutagenesis)	1 ді
	Ex Taq (Takara Shuzo)	0.5 µl
PCR 2	10X Ex Taq Buffer (Takara Shuzo)	10 µl
	2.5 mM solution of dNTPs	8 μί
	the plasmid vector described in EXAMPLE 11 (8ng/ml)	الب 2
	sterile distilled water	73.5 µl
	20 μM solution of primer 3	ا لبر 5
	100 μM solution of primer 4 (for mutagenesis)	ابر 1
	Ex Taq (Takara Shuzo)	0.5 μl

Specific sets of primers were used for each mutation and other components were unchanged. Primers used for the reactions are shown in Table 10. The nucleotide sequences of the primers are shown in SEQUENCE NO: 20,23,27 and 30-40. The PCRs were performed under the following conditions as follows. An initial denaturation step at 97°C for 3 min was followed by 25 cycles of denaturation at 95°C for 1 min annealing at 55°C for 1 min and extension at 72°C for

2.0

3 min. After these amplification cycles, final extension was performed at 70°C for 5 min. The size of the PCR products was confirmed by agarose gel electrophoresis using reaction solution. After the first PCR, excess primers were removed using Amicon microcon (Amicon). The final volume of the solutions that contained the PCR products were made to 50µl with sterile distilled water. These purified PCR products were used for the second PCR (PCR 3).

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PCR3	10X Ex Taq Buffer (Takara Shuzo)	ابر 10
1	2.5 mM solution of dNTPs	ابر 8
	solution containing DNA fragment obtained from PCR 1	5 µl
	solution containing DNA fragment obtained from PCR 2	5 µl
	sterile distilled water	61.5 யி
	20 μM solution of primer 1	5 µl
	20 μM solution of primer 3	5 μl
	Ex Taq (Takara Shuzo)	0.5 μl

Table 10

mutants	primer-1	primer-2	primer-3	primer-4
OCIF-C19S	IF 10	C19SR	IF 3	C19SF
OCIF-C20S	IF 10	C20SR	IF 3	C20SF
OCIF-C21S	IF 10	C21SR	IF3.	C21SF
OCIF-C22S	IF 10	C22SR	IF 14	C22SF
OCIF-C23S	IF 6	C23SR	IF 14	C23SF

The reaction conditions were exactly the same as those for PCR 1 or PCR 2. The size of the PCR prodcts was confirmed by 1.0 % or 1.5 % agarose gel electrophoresis. The DNA fragments were precipitated with ethanol, dried under vacuum and dissolved in 40 µl of sterile distilled water. The solutions containing DNA fragments with mutation C19S, C20S, C21S, C22S and C23S were designated as DNA solution A, DNA solution B, DNA solution C, DNA solution D and DNA solution E, respectively.

The DNA fragment which is contained in solution A (20μl) was digested with restriction enzymes Nde I and Sph I (Takara Shuzo). A DNA fragment with an approximate size of 400 base pairs (bp) was extracted from a preparative agarose gel and dissolved in 20 μl of sterile distilled water. This DNA solution was designated DNA solution 3. Two micrograms of pSK + -OCIF was digested with restriction enzymes Nde I and Sph I. A DNA fragment with an approximate size of 4.2 kb was purified from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μl of sterile distilled water. This DNA solution was designated as DNA solution 4. Two microliters of DNA solution 3, 3 μl of DNA solution 4 and 5 μl of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 αcells were transformed with 5 μl of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-C19S.

The DNA fragment which is contained in solution B (20 μ) was digested with restriction enzymes Nde I and Sph I. A DNA fragment with an approximate size of 400 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated DNA solution 5. Two microliters of DNA solution 5, 3 μ I of DNA solution 4 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-C20S. The DNA fragment which is contained in solution C (20 μ I) was digested with restriction enzymes Nde I and Sph I. A DNA fragment with an approximate size of 400 bp was extracted from a preparative agarose gel with QIAEX gel extrac-

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tion kit and dissolved in 20µl of sterile distilled water. This DNA solution was designated as DNA solution 6. Two micro-

liters of DNA solution 6, 3 μ l of DNA solution 4 and 5 μ l of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ l of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-C21S.

The DNA fragment which is contained in solution D (20 μ) was digested with restriction enzymes Nde I and Bst PI. A DNA fragment with an approximate size of 600 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 7. Two micrograms of pSK + -OCIF was digested with restriction enzymes Nde I and Bst PI. A DNA fragment with an approximate size of 4.0 kb was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 8. Two microliters of DNA solution 7, 3 μ I of DNA solution 8 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 μ I cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA in which the 600-bp Nde I-BstPI fragment with the mutation (the C22S mutation) is substituted for the 600-bp Nde I-Bst PI fragment of pSK+-OCIF by analyzing the DNA structure. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-C22S.

The DNA fragment which is contained in solution E (20 μ I) was digested with restriction enzymes Bst PI and Eco RV. A DNA fragment with an approximate size of 120 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 9. Two micrograms of pSK + -OCIF was digested with restriction enzymes Bst EII and Eco RV. A DNA fragment with an approximate size of 4.5 kb was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 10. Two microliters of DNA solution 9, 3 μ I of DNA solution 10 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation was carried out. Competent E. coli DH5 α cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-C23S.

2) Construction of vectors for expressing the OCIF mutants

pSK-OCIF-C20S, pSK-OCIF-C20S, pSK-OCIF-C21S, pSK-OCIF-C22S and pSK-OCIF-C23S were digested with restriction enzymes Bam HI and Xho I. The 1.6 kb Bam HI-Xho I DNA fragment encoding each OCIF mutant was isolated and dissolved in 20μl of sterile distilled water. The DNA solutions that contain 1.6 kb cDNA fragments derived from pSK-OCIF-C19S, pSK-OCIF-C20S, pSK-OCIF-C21S, pSK-OCIF-C22S and pSK-OCIF-C23S were designated C19S DNA solution, C20S DNA solution, C20S DNA solution, C20S DNA solution, respectively. Five micrograms of a expression vector pCEP 4 (Invitrogen) was digested with restriction enzymes Bam HI and Xho I. A DNA fragment with an approximate size of 10 kb was purified and dissolved in 40μl of sterile distilled water. This DNA solution was designated as pCEP 4 DNA solution. One microliter of pCEP 4 DNA solution and 6 μl of either C19SDNA solution, C20S DNA solution, C21S DNA solution, C22S DNA solution or C23S DNA solution were independently mixed with 7 μl of ligation buffer I of DNA ligation kit ver. 2 and ligation reactions were carried out. Competent E. coli DH5α cells (100μl) were transformed with 7 μl of each ligation mixture. Ampicillin-resistant transformants were screened for clones containing plasmid in which a 1.6-kb cDNA fragment is inserted between the recognition sites of Bam HI and Xho I of pCEP 4 by analyzing the DNA structure. The plasmide which were obtained containing the cDNA encoding OCIF-C19S, OCIF-C20S, OCIF-C21S, OCIF-C22S and OCIF-C23S, respectively.

ii) Preparation of domain-deletion mutants of OCIF

(1) deletion mutagenesis of OCIF cDNA

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A series of OCIF mutants with deletions of from Thr 2 to Ala 42, from Pro 43 to Cys 84, from Glu 85 to Lys 122, from Arg 123 to Cys 164, from Asp 177 to Gln 251 and from Ile 252 to His 326 were prepared (positions of the amino acid residues are shown in SEQUENCE NO: 4). These mutants were designated as OCIF-DCR1, OCIF-DCR2, OCIF-DCR3, OCIF-DCR4, OCIF-DDD1 and OCIF-DDD2, respectively.

Mutagenesis was performed by two-step PCR as described in EXAMPLE 22-(ii). The primer sets for the reactions are shown in Table 11 and the nucleotide sequences of the primers are shown in SEQUENCE NO: 19, 25, 40-53, and 54.

Table 11

mutants	primer-1	primer-2	primer-3	primer-4
OCIF-DCR1	Xhoi F	DCR1R	IF 2	DCR1F
OCIF-DCR2	Xhoi F	DCR2R	IF 2	DCR2F
OCIF-DCR3	Xhol F	DCR3R	IF 2	DCR3F
OCIF-DCR4	Xhol F	DCR4R	IF 16	DCR4F
OCIF-DDD1	IF8	DDD1R	IF 14	DDD1F
OCIF-DDD2	IF8	DDD2R	IF 14	DDD2F

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The final PCR products were precipitated with ethanol, dried under vacuum and dissolved in 40µl of sterile distilled water. Solutions of DNA fragment coding for portions of OCIF-DCR1, OCIF-DCR2, OCIF-DCR3, OCIF-DCR4, OCIF-DDD1 and OCIF-DDD2 were designated as DNA solutions F, G, H, I, J and K, respectively.

The DNA fragment which is contained in solution F (20 μ) was digested with restriction enzymes Nde I and Xho I. A DNA fragment with an approximate size of 500 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated DNA solution 11. Two micrograms of pSK+-OCIF was digested with restriction enzymes Nde I and Xho I. A DNA fragment with an approximate size of 4.0 kb was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated DNA solution 12. Two microliters of DNA solution 11, 3 μ I of DNA solution 12 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation was carried out. Competent E. coli DH5 α cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DCR1.

The DNA fragment which is contained in solution G (20 μ I) was digested with restriction enzymes Nde I and Xho I. A DNA fragment with an approximate size of 500 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 13. Two microliters of DNA solution 13, 3 μ I of DNA solution 12 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation was carried out. Competent E. coli DH5a cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing plasmid DNA . DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DCR2.

The DNA fragment which is contained in solution H (20 μ l) was digested with restriction enzymes Nde I and Xho I. A DNA fragment with an approximate size of 500 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ l of sterile distilled water. This DNA solution was designated as DNA solution 14. Two microliters of DNA solution 14, 3 μ l of DNA solution 12 and 5 μ l of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ l of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DCR3.

The DNA fragment which is contained in solution I (20 μ I) was digested with restriction enzymes Xho I and Sph I. A DNA fragment with an approximate size of 900 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 15. Two micrograms of pSK+ -OCIF was digested with restriction enzymes Xho I and Sph I. A DNA fragment with an approximate size of 3.6 kb was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 16. Two microliters of DNA solution 15, 3 μ I of DNA solution 16 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DCR4.

The DNA fragment which is contained in solution J (20 μ I) was digested with restriction enzymes BstP I and Nde I. A DNA fragment with an approximate size of 400 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ I of sterile distilled water. This DNA solution was designated as DNA solution 17. Two microliters of DNA solution 17, 3 μ I of DNA solution 8 and 5 μ I of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ I of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by

restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DDD1. The DNA fragment which is contained in solution K (20 μ l) was digested with restriction enzymes Nde I and BstP I. A DNA fragment with an approximate size of 400 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20 μ l of sterile distilled water. This DNA solution was designated as DNA solution 18. Two microliters of DNA solution 18, 3 μ l of DNA solution 8 and 5 μ l of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5 μ l of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-DDD2.

2) Construction of vectors for expressing the OCIF mutants

pSK-OCIF-DCR1, pSK-OCIF-DCR2, pSK-OCIF-DCR3, pSK-OCIF-DCR4, pSK-OCIF-DDD1 and pSK-OCIF-DDD2 were digested with restriction enzymes Bam HI and Xho I. The Bam HI-Xho I DNA fragment containing entire coding sequence for each OCIF mutant was isolated and dissolved in 20 μl of sterile distilled water. These DNA solutions that contain the Bam HI-Xho I fragment derived from pSK-OCIF-DCR1, pSK-OCIF-DCR2, pSK-OCIF-DCR3, pSK-OCIF-DCR4, pSK-OCIF-DDD1 and pSK-OCIF-DDD2 were designated DCR1 DNA solution, DCR2 DNA solution, DCR3 DNA solution, DCR4 DNA solution, DDD1 DNA solution, DDD1 DNA solution, DDD2 DNA solution, DCR3 DNA solution, DCR4 DNA solution, DCR4 DNA solution, DCR4 DNA solution, DDD1 DNA solution or DDD2 DNA solution were independently mixed with 7μl of ligation buffer I of DNA ligation kit ver. 2 and ligation reactions were carried out. Competent E. coli DH5α cells (100 μl) were transformed with 7 μl of each ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA in which the DNA fragment with deletions is inserted between the recognition sites of Bam HI and Xho I of pCEP 4 by analyzing the DNA structure. The plasmids containing the cDNA encoding OCIF-DCR1, OCIF-DCR2, OCIF-DCR3, OCIF-DCR4, OCIF-DDD1 and OCIF-DDD2 were designated as pCEP4-OCIF-DCR1, pCEP4-OCIF-DCR2, pCEP4-OCIF-DCR3, pCEP4-OCIF-DCR4, pCEP4-OCIF-DDD1 and pCEP4-OCIF-DDD2, respectively.

- iii) Preparation of OCIF with C-terminal domain truncation
- (1) mutagenesis of OCIF cDNA

A series of OCIF mutants with deletions of from Cys at amino acid residue 379 to Leu 380, from Ser 331 to Leu 380, from Asp 252 to Leu 380, from Asp 177 to Leu 380, from Arg 123 to Leu 380 and from Cys 86 to Leu 380 was prepared. Positions of the amino acid residues are shown in SEQUENCE NO: 4. These mutants were designated as OCIF-CL, OCIF-CDD2, OCIF-CDD1, OCIF-CCR4 and OCIF-CCR3, respectively.

Mutagenesis for OCIF-CL was performed by the two-step PCR as described in EXAMPLE 22-(ii). The primer set for the reaction is shown in Table 12. The nucleotide sequences of the primers are shown in SEQUENCE NO:23, 40, 55, and 56. The final PCR products were precipitated with ethanol, dried under vacuum and dissolved in 40µl of sterile distilled water. This DNA solution was designated as solution L.

The DNA fragment which is contained in solution L (20 μl) was digested with restriction enzymes BstP I and EcoR V. A DNA fragment with an approximate size of 100 bp was extracted from a preparative agarose gel with QIAEX gel extraction kit and dissolved in 20μl of sterile distilled water. This DNA solution was designated as DNA solution 19. Two microliters of DNA solution 19, 3 μl of DNA solution 10 (described in EXAMPLE 22-(ii)) and 5μl of ligation buffer I of DNA ligation kit ver. 2 were mixed and ligation reaction was carried out. Competent E. coli DH5 α cells were transformed with 5μl of the ligation mixture. Ampicillin-resistant transformants were screened for a clone containing a plasmid DNA. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmid thus obtained was named pSK-OCIF-CL Mutagenesis of OCIF cDNA to prepare OCIF-CC, OCIF-CDD2, OCIF-CDD1, OCIF-CCR4 and OCIF-CCR3 was performed by a one-step PCR.

PCR reactions for mutagenesis to prepare OCIF-CC, OCIF-CDD2, OCIF-CDD1, OCIF-CCR4 and OCIF-CCR3

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10 X Ex Taq Buffer (Takara Shuzo)

2.5 mM solution of dNTPs

the plasmid vector containing the entire OCIF cDNA described in EXAMPLE 11 (8ng/ml)

sterile distilled water

20 μM solution of primer OCIF Xho F

100 μM solution of primer (for mutagenesis)

Ex Taq (Takara Shuzo)

10 μl

8 μl

73.5 μl

73.5 μl

1 μl

0.5 μl

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Table 12

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mutants	primer-1	primer-2	primer-3	primer-4
OCIF-CL	IF6	CL R	IF 14	CLF

Specific primers were used for each mutagenesis and other components were unchanged.

Primers used for the mutagenesis are shown in Table 13. Their nucleotide sequences are shown in SEQUENCE NO:57-61. The components of each PCR were mixed in a microcentrifuge tube and PCR was performed as follows. The microcentrifuge tubes were treated for 3 minutes at 97 °C and then incubated sequentially, for 30 seconds at 95 °C, 30 seconds at 50 °C and 3 minutes at 70 °C. This three-step incubation procedure was repeated 25 times, and after that, the tubes were incubated for 5 minutes at 70 °C. An aliquot of the reaction mixture was removed from each tube and analyzed by an agarose gel electrophoresis to confirm the size of each product.

The size of the PCR products was confirmed on an agarose gel. Excess primers in the PCRs were removed using Amicon microcon (Amicon) after completion of the reaction. The DNA fragments were precipitated with ethanol, dried under vacuum and dissolved in 40 μ l of sterile distilled water. The DNA fragment in each DNA solution was digested with restriction enzymes Xho I and Bam HI. After the reactions, DNA was precipitated with ethanol, dried under vacuum and dissolved in 20 μ l of sterile distilled water.

The solutions containing DNA fragment with the CC deletion, the CDD2 deletion, the CDD1 deletion, the CCR4 deletion and the CCR3 deletion were designated as CC DNA solution, CDD2 DNA solution, CDD1 DNA solution, CCR4 DNA solution and CC R3 DNA solution, respectively.

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Table 13

mutants	primers for the mutagenesis
OCIF-CC	CC R
OCIF-CDD2	CDD2 R
OCIF-CDD1	CDD1 R
OCIF-CCR4	CCR4 R
OCIF-CCR3	CCR3 R

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(2) Construction of vectors for expressing the OCIF mutants

pSK-OCIF-CL was digested with restriction enzymes Barn HI and Xho I. The Barn HI-Xho I DNA fragment containing the entire coding sequence for OCIF-CL was isolated and dissolved in 20 µI of sterile distilled water. This DNA solution was designated as CL DNA solution. One microliter of pCEP 4 DNA solution and 6 µI of either of CL DNA solution, CC DNA solution, CDD2 DNA solution, CDD1 DNA solution, CCR4 DNA solution or CCR3 DNA solution were independently mixed with 7 µI of ligation buffer I of DNA ligation kit ver. 2 and ligation reactions were carried out. Competent

E. coli DH5α cells (100 μl) were transformed with 7 μl of each ligation mixture. Ampicillin-resistant transformants were screened for clones containing plasmids which have the desirable mutations in OCIF cDNA by analyzing the DNA structure. In each plasmid, OCIF cDNA fragment having a deletion were inserted between the recognition sites of Xho I and Bam HI of pCEP 4. The plasmids containing the cDNA encoding OCIF-CL, OCIF-CC, OCIF-CDD1, OCIF-CDD2, OCIF-CCR4 and OCIF-CCR3 were designated pCEP4-OCIF-CL, pCEP4-OCIF-CC, pCEP4-OCIF-CDD2, pCEP4-OCIF-CDD1, pCEP4-OCIF-CCR4 and pCEP4-OCIF-CCR3, respectively.

- iv) Preparation of OCIF mutants with C-terminal truncation
- (1) Introduction of C-terminal truncation to OCIF

A series of OCIF mutants with C-terminal truncation was prepared. OCIF mutant in which 10 residues of from Gin at 371 to Leu at 380 are replaced with 2 residues of Leu-Val was designated OCIF-CBst. OCIF mutant in which 83 residues of from Cys 298 to Leu 380 are replaced with 3 residues of Ser-Leu-Asp was designated OCIF-CSph. OCIF mutant in which 214 residues of from Asn 167 to Leu 380 are removed was designated OCIF-CBsp. OCIF mutant in which 319 residues of from Asp 62 to Leu 380 are replaced with 2 residues of Leu-Val was designated OCIF-CPst. Positions of the amino acid residues are shown in SEQUENCE NO: 4.

Two micrograms each of pSK + -OCIF was digested with one of the restriction enzymes, Bst PI, Sph I, Pstl (Takara Shuzo), and Bsp EI (New England Biolabs), and followed by phenol extraction and ethanol precipitation. The precipitated DNA was dissolved in 10 μ I of sterile distilled water. Ends of the DNAs in 2 μ I of each solution were blunted using a DNA blunting kit in final volumes of 5 μ I. To the reaction mixtures, 1 μ g (1 μ I) of an Amber codon-containing Xba I linker (5'-CTAGTCTAGACTAG-3') and 6 μ I of ligation buffer I of DNA ligation kit ver. 2 were added.

After the ligation reactions, $6 \mu l$ each of the reaction mixtures was used to transform E. coli DH5 α . Ampicillin-resistant transformants were screened for clones containing plasmids. DNA structure was analyzed by restriction enzyme mapping and by DNA sequencing. The plasmids thus obtained were named pSK-OCIF-CBst, pSK-OCIF-CSph, pSK-OCIF-CBsp and pSK-OCIF-CPst, respectively.

- (2) Construction of vectors for expressing the OCIF mutants
- pSK-OCIF-CBst, pSK-OCIF- CSph, pSK-OCIF-CBsp and pSK-OCIF-CPst were digested with restriction enzymes Bam HI and Xho I. The 1.5 kb of DNA fragment containing entire coding sequence for each OCIF mutant was isolated and dissolved in 20 μl of sterile distilled water. These DNA solutions that contain the Bam HI-XhoI fragment derived from pSK-OCIF-CBst, pSK-OCIF- CSph, pSK-OCIF-CBsp and pSK-OCIF-CPst were designated as CBst DNA solution, CSph DNA solution, CBsp DNA solution and CPst DNA solution, respectively. One microliter of pCEP 4 DNA solution (described in EXAMPLE 22-ii)) and 6 μl of either CBst DNA solution, CSph DNA solution, CBsp DNA solution or CPst DNA solution were independently mixed with 7 μl of ligation buffer I of DNA ligation kit ver. 2 and ligation reactions were carried out. Competent E. coli DH5α cells (100 μl) were transformed with 7 μl of each ligation mixture. Ampicillin-resistant transformants were screened for dones containing plasmids in which cDNA fragment is inserted between the recognition sites of Bam HI and Xho I of pCEP 4 by analyzing the DNA structure. The plasmids containing the cDNA encoding OCIF-CBst, OCIF-CBsp and OCIF-CPst were designated as pCEP4-OCIF-CBst, pCEP4-OCIF-CSph, pCEP4-OCIF-CBst, pCEP4-OCIF-CPst, respectively.
 - v) Preparetion of vectors for expressing the OCIF mutants

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- E. coli clones harboring the expression vectors for OCIF mutants (total of 21 clones) were grown and the vectors were purified by QIAGEN column (QIAGEN). All the expression vectors were precipitated with ethanol and dissolved in appropriate volumes of sterile distilled water and used for further manipupations shown below.
 - vi) Transient expression of the cDNAs for OCIF mutants and biological activities of the mutants

OCIF mutants were produced using the expression vectors prepared in EXAMPLE 22-v). The method was essentially the same as described in EXAMPLE 13. Only the modified points are described below. A 24-well plate was used for the DNA transfection. 2X10⁵ cells of 293/EBNA suspended in IMDM containing 10% fetal bovine serum were seeded into each well of the plate. One microgram of purified vector DNA and 4µl of lipofectamine were used for each transfection. Mixture of an expression vector and lipofectamine in OPTI-MEM (GIBCO BRL) in a final volume of 0.5 ml was added to the cells in a well. After the cells were incubated at 37°C for 24 hr in a CO₂ incubator, the medium was replaced with 0.5 ml of Ex-cell 301 medium (JSR). The cells were incubated at 37 °C for 48 more hours in the CO₂ incubator. The conditioned medium was collected and used for assay for in vitro biological activity. The nucleotide

sequences of cDNAs for the OCIF mutants are shown in SEQUENCE NO:83-103. The deduced amino acid sequences for the OCIF mutants are shown in SEQUENCE NO: 62-82. The assay for in vitro biological activity was performed as described in EXAMPLE 13. Antigen concentration of each conditioned medium was determined by ELISA as described in EXAMPLE 24. Table 14 shows specific activity of the mutants relative to that of the unaltered OCIF.

Table 14

Table 14										
mutants	activity									
the unaltered OIF	++									
OCIF-C19S	+									
OCIF-C20S	±									
OCIF-C21S	±									
OCIF-C22S	+									
OCIF-C23S	++									
OCIF-DCR1	± .									
OCIF-DCR2	±									
OCIF-DCR3	±									
OCIF-DCR4	±									
OCIF-DDD1	+									
OCIF-DDD2	±									
OCIF-CL	++									
OCIF-CC	. ++									
OCIF-CDD2	++									
OCIF-CDD1	+									
OCIF-CCR4										
OCIF-CCR3	±									
OCIF-CBst	++									
OCIF-CSph	++									
OCIF-CBsp	±									
OCIF-CPst	±									
	±									

⁺⁺ indicates relative activity more than 50% of that of the unaltered OCIF

vii) western blot analysis

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Ten microliters of the final conditioned medium was used for western blot analysis. Ten microliters of the sample were mixed with 10 µl of SDS-PAGE sample buffer (0.5 M Tris-HCl, 20% glycerol, 4% SDS, 20µg/ml bromo phenol blue, pH 6.8) boiled for 3 min. and subjected to a 10 % SDS polyacryl amide gel electrophoresis under non-reducing conditions. After the electrophoresis, the separated proteins were blotted to PVDF membrane (ProBlott^R, Perkin Elmer) using a semi-dry electroblotter (BIO-RAD). The membrane was incubated at 37°C with horseradish peroxidase labeled anti-OCIF antibodies for 2 hr. After the membrane was washed, protein bands which react with the labeled antibodies were detected using ECL system (Amersham). Two protein bands with approximate molecular masses of 60kD and 120kD were detected for the unaltered OCIF. On the other hand, almost exclusively 60kD protein band was detected for OCIF-C23S, OCIF-CL and OCIF CC. Protein bands with an approximate masses of 40kD-50kD and 30kD-40kD were the major ones for OCIF-CDD2 and OCIF-CDD1, respectively. These results indicate that Cys at 379 is responsible for the dimer formation, both the monomers and the dimers maintain the biological activity and a deletion of residues from Asp

 $[\]pm$ indicates relative activity between 10% and 50% \pm indicates relative activity less than 10%, or production level too low to determine the accurate biological activity

at 177 to Leu at 380 does not abolish the biological activity of OCIF (positions of the amino acid resare shown in SEQUENCE NO: 4).

EXAMPLE 23

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Isolation of human genomic OCIF gene

i) Screening of a human genomic library

An amplified human placenta genomic library in Lambda FIX II vector purchased from STRATAGENE was screened for the gene encoding human OCIF using the human OCIF cDNA as a probe. Essentially, screening was done according to the instruction manual supplied with the genomic library. The basic protocols described in Molecular Cloning: A Laboratory Manual also were employed to manipulate phage, E. coli, and DNA.

The library was titered, and 1x10⁶ pfu of phage was mixed with XL1-Blue MRA host E. coli cells and plated on 20 plates (9 cm x 13 cm) with 9 ml per plate of top agarose. The plates were incubated overnight at 37°C. Filter plaque lifts were prepared using Hybond-N nyton membranes (Amersham). The membranes were processed by denaturation in a solution containing 1.5 M NaCl and 0.5 M NaOH for 1 minute at room temperature. The membranes were then neutralized by placing successively for one minute each in 1 M Tris-HCl (pH7.5) and a solution containing 1.5 M NaCl and 0.5 M Tris-HCl (pH 7.5). The membranes were then transferred onto a filter paper wet with 2xSSC. Phage DNA was fixed on the membranes with 1200µJoules of UV energy in STRATALINKER UV crosslinker 2400 (STRATAGENE) and the membranes were air dried. The membranes were immersed in Rapid Hybridization buffer (Amersham) and incubated for one hour at 65 °C before hybridization with 32P-labeled cDNA probe in the same buffer overnight at 65°C. Screening probe was prepared by labeling the OCIF cDNA with ³²P using the Megaprime DNA labeling system (Amersham). Approximately, 5x10⁵cpm probe was used for each ml of hybridization buffer. After the hybridization, the membranes were rinsed in 2xSSC for five minutes at room temperature. The membranes were then washed four times, 20 minutes each time, in 0.5xSSC containing 0.1 % SDS at 65 °C. After the final wash, the membranes were dried and subjected to autoradiography at -80 °C with SUPER HR-H X-ray film (FUJI PFOTO FILM Co., Ltd.) and an intensifying screen. Upon examination of the autoradiograms, six positive signals were detected. Agar plugs were picked from the regions corresponded to these signals for phage purification. Each agar plug was soaked overnight in 0.5 ml of SM buffer containing 1% chloroform to extract phage. Each extract containing phage was diluted 1000 fold with SM buffer and an aliquot of 1 ml or 20 ml was mixed with host E. coli described above. The mixture was plated on agar plates with top agarose as described above. The plates were incubated overnight at 37 °C, and filter lifts were prepared, prehybridized, hybridized, washed and autoradiographed as described above. This process of phage purification was applied to all six positive signals initially detected on the autoradiograms and was repeated until all phage plaques on agar plates hybridize with the cDNA probe. After purification, agar plugs of each phage isolate were soaked in SM buffer containing 1% chloroform and stored at 4 °C. Six individual phage isolates were designated λ OIF3, λ OIF9, λ OIF11, λ OIF12 and λ OIF17, respectively.

ii) Analysis of the genomic clones by restriction enzyme digestion and Southern blot hybridization

DNA was prepared from each phage isolate by the plate lysate method as described in Molecular Cloning: A Laboratory Manual. DNA prepared from each phage was digested with restriction enzymes and the fragments derived from the digestion were separated on agarose gels. The fragments were then transferred to nylon membranes and subjected to Southern blot hybridization using OCIF cDNA as a probe. The results of the analysis revealed that the six phage isolates are individual clones. Among these fragments derived from the restriction enzyme digestion, those fragments which hybridized with the OCIF cDNA probe were subcloned into plasmid vectors and subjected to the nucleotide sequence analysis as described below.

iii) Subcloning restriction fragments derived from genomic clones into plasmid vectors and determination of the nucleotide sequence.

 λ OIF8 DNA was digested with restriction enzymes EcoRI and NotI, and the DNA fragments derived these from were separated on a 0.7% agarose gel. The 5.8 kilobase pairs (kb) EcoRI/NotI fragment was extracted from the gel using QIAEX II Gel Extraction·Kit (QIAGEN) according to the procedure recommended by the manufacturer. The 5.8 kb EcoRI/NotI fragment was ligated with pBluescript II SK+ vector (STRATAGENE) which had been linearized with restriction enzymes EcoRI and NotI, using Ready-To-Go T4 DNA Ligase (Pharmacia) according to the procedure recommended by the manufacturer. Competent DH5 α E. coli cells (Amersham) were transformed with the recombinant plasmid and transformants were selected on L-plates containing 50 µg/ml of ampicillin. A clone harboring the recom-

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EXAMPLE 26

Therapeutic effect on osteoporosis

5 (1) Method

Male Fischer rats, 6 weeks-old, were subjected to denervation of left forelimb. These rats were assigned to four groups(10 rats/group) and treated as follows; group A, sham operated rats without administration; group B, denervated rats with intravenous administration of vehicle; group C, denervated rats administered OCIF intravenously at a dose of 5 μ g/kg twice a day; group D, denervated rats administered OCIF intravenously at a dose of 50 μ g/kg twice a day. After denervation, OCIF was administered daily for 14 days. After 2 weeks treatment, the animals were sacrificed and their forelimbs were dissected. Thereafter bones were tested for mechanical strength.

(2) Results

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Decrease of bone strength was observed in the animals of control groups as compared to those animals of the normal groups while bone strength was increase in the groups of animal received 50 mg of OCIF per kg body weight.

Industrial availability

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The present invention provides both a novel protein which inhibits formation of osteoclasts and a efficient procedure to produce the protein. The protein of the present invention has an activity to inhibit formation of osteoclasts. The protein will be useful for the treatment of many diseases accompanying bone loss, such as osteoporosis, and as an antigen to be used for the immunological diagnosis of such diseases.

Referring to the deposited the microorgainsm

Name and Address of the Depositary Authority

Name:

National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology Ministry of International Trade and Industry

Address:

1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 305, JAPAN

Deposited date:

June 21, 1995

(It was transferred from Bikkoken No. P-14998, which was deposited on June 21, 1995.

Transferred date: October 25, 1995)

Acession Number: FERM BP-5267

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50

	SEQUENCE LISTING
_	(1) GENERAL INFORMATION:
5	(i) APPLICANT:
	(A) NAME: SNOW BRANDS MILK PRODUCTS CO., LTD.
	(B) STREET:
10	(C) CITY:
	(D) STATE:
	(E) COUNTRY:
5	(F) POSTAL CODE (ZIP):
	(G) TELEPHONE:
	(H) TELEFAX:
o	(I) TELEX:
	(ii) TITLE OF INVENTION: Novel proteins and methods for producing the
	proteins
5	(iii) NUMBER OF SEQUENCES: 105
-	(iv) COMPUTER READABLE FORM:
	(A) MEDIUM TYPE: Floppy disk
	(B) COMPUTER:
7	(C) OPERATING SYSTEM:
	(D) SOFTWARE: Wordperfect windows
	(V) CURRENT APPLICATION DATA:
ī	(A) APPLICATION NUMBER: JP (B) FILE REFERENCE:
	(C) FILING DATE:
	(O) FILING DATE.

(2) INFORMATION FOR SEQUENCE ID NO: 1:

	(1) SEQUENCE CHARACTERISTICS:
5	(A) LENGTH: 6
	(B) TYPE: amino acid
	(D) TOPOLOGY : linear
10	(ii) MOLECULE TYPE: peptide (an internal amino acid sequence of the
	protein)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 1:
	Xaa Tyr His Phe Pro Lys
15	1 5
	(2) INFORMATION FOR SEQUENCE ID NO: 2:
20	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 14
	(B) TYPE: amino acid
	(D) TOPOLOGY : linear
25	(ii) MOLECULE TYPE : peptide (an internal amino acid sequence of the
	protein)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO:2:
20	Xaa Gln His Ser Xaa Gln Glu Gln Thr Phe Gln Leu Xaa Lys
	1 5 10
	(2) INFORMATION FOR SEQUENCE ID NO: 3:
5	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 12.
	(B) TYPE: amino acid
0	(D) TOPOLOGY : linear
-	(ii) MOLECULE TYPE : peptide (an internal amino acid sequence of the
	protein)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 3:
5	Xaa Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys
	1 5 10
2	(2) INFORMATION FOR SEQUENCE ID NO: 4:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 380
5	·

		(B)	TYPE	: a	mina	aci	d							•	
		(D)	TOPO	LOGY	: 1	inea	r								
5	(ii)	MOLE	CULE	TYP	E :	prot	ein	(OCI	F pr	otei	n wi	thou	t si	gnal	peptide)
	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	NO:	4:					
	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His	Tyr	Asp	Glu	Glu	Thr	Ser
10	1				5					10					15
	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro	Pro	Gly	Thr	Tyr	Leu	Lys
					20					25					30
45	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr	Val	Cys	Ala	Pro	Cys	Pro
15			_	_	35					40				÷	45
	Asp	His	Tyr	Tyr		Asp	Ser	Trp	His		Ser	Asp	Glu	Cys	Leu
		_	^	_	50	_				55	_				60
20	iyr	Cys	Ser	Pro		Cys	Lys	Glu	Leu		Tyr	Val	Lys	Gln	
	C	۸	A	Th	65	A	4	17 - 1	C	70	~		01		75
	Cys	ASD	Arg	Thr	n1s 80	Asn	Arg	val	cys		Cys	Lys	Glu	Gly	_
25	Tvr	Len	Glu	Ile		Phe	Cve	Lou	Īve	85 u	A ===	S	Cua	Dona	90 Pma
	1,1	LCU	OIU	116	95	I IIC	C)S	Leu	Lys	100	ALE	Ser	cys	rro	
•	Glv	Phe	Glv	Val		G1n	Ala	G1 v	Thr		Glu	Ara	Acn	Thr	105 Val
	,		,		110		*****	01,	****	115	010	ur E	ASH	ш	120
30	Cys	Lys	Arg	Cys		Asp	Gly	Phe	Phe		Asn	Glu	Thr	Ser	
					125	•	•			130					135
	Lys	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn		Ser	Val	Phe	Gly	
35					140					145				•	150
	Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr	His	Asp	Asn	Ile	Cys	Ser
					155					160					165
40	Gly	Asn	Ser	Glu	Ser	Thr	Gln	Lys	Cys	Gly	Ile	Asp	Val	Thr	Leu
		-			170					175					180
	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala	Val	Pro	Thr	Lys	Phe	Thr
					185					190					195
45	Pro	Asn	Trp	Leu	Ser	Val	Leu	Val	Asp	Asn	Leu	Pro	Gly	Thr	Lys
					200					205					210
	Val	Asn	Ala	G1u		Val	Glu	Arg			Arg	G1n	His	Ser	Ser
50	a :				215		_			220					225
	GIn	Glu	GIn	Thr		Gln	Leu	Leu	Lys	Leu	Trp	Lys	His	Gln	Asn
					230					235		-			240

	Lys Asp Gln Asp Ile Val Lys Lys Ile Ile Gln Asp Ile Asp Leu														
5	245 250 255														
	Cys Glu Asn Ser Val Gln Arg His Ile Gly His Ala Asn Leu Thr														
	260 265 270														
40	Phe Glu Gln Leu Arg Ser Leu Met Glu Ser Leu Pro Gly Lys Lys														
10	275 280 285														
	Val Gly Ala Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys Lys Pro														
	290 295 300														
15	Ser Asp Gln Ile Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys Asn														
	305 310 315														
	Gly Asp Gln Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His	•													
	320 325 330														
20	Ser Lys Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys														
	335 340 345														
	Lys Thr Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr 350 355 360														
25	350 355 360 Gln Lys Leu Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val														
	365 370 375														
	Lys Ile Ser Cys Leu														
30	380														
30	(2) INFORMATION FOR SEQUENCE ID NO: 5:														
	(i) SEQUENCE CHARACTERISTICS:														
	(A) LENGTH: 401														
35	(B) TYPE: amino acid														
	(D) TOPOLOGY :: linear														
	(ii) MOLECULE TYPE: protein (OCIF protein with signal peptide	e)													
40	(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 5:														
	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser														
	-20 -15 -10														
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His														
45	-5 -i 1 5														
	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro														
	10 15 20														
50	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr														
<i>5</i> 0	25 30 35														
	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His														

	40					45					50				
•	Thr	Ser	Asp	Glu	Cys	Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu
5	55					60					65				
	Gln	Tyr	Val	Lys	Gln	Glu	Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
	70	•				7 5					80			÷	
10	Glu	Cys	Lys	Glu	Gly	Arg	Tyr	Leu	Glu	Ile	Glu	Phe	Cys	Leu	Lys
	85					90					95				
	His	Arg	Ser	Cys	Pro	Pro	Gly	Phe	Gly	Val	Val	Gln	Ala	Gly	Thr
15	100					105					110				
	Pro	Glu	Arg	Asn	Thr	Val	Cys	Lys	Arg	Cys	Pro	Asp	Gly	Phe	Phe
	115					120					125				
		Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn
20	130					135					140				
		Ser	Val	Phe	Gly		Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr
	145					150					155				
25		Asp	Asn	Ile	Cys		Gly	Asn	Ser	Glu		Thr	G1n	Lys	Cys
	160	71		, ,	- -1	165	_				170				
		116	Asp	vai	inr		Cys	Glu	GLU	Ala		Phe	Arg	Phe	Ala
	175	Dma	Thu	1	DL.	180	D	A	т	T	185	17. 1		· ·	
30	190	110	Thr	Lys	rne	195	FIO	ASII	irp	Leu		val	Leu	vaı	Asp
		Ĺen	Pro	G] v	The		V ₂ 1	Acn	Ala	G1,,	200	Va 1	C1	A	T1a
	205	204		u,	****	210	141	Man	VIG	olu	215	141	ulu	VT R	
	Lys	Arg	G1n	His	Ser		Gln	Glu	Gln	Thr		G1 n	Len	Leu	Lvs
	220					225					230	U1	200	Dou	0 ,0
	Leu	Trp	Lys	His	Gln		Lys	Asp	Gln	Asp		Val	Lvs	Lvs	Ile
	235					240	•	-		•	245		•	•	
40	Ile	Gln	Asp	Ile	Asp	Leu	Cys	Glu	Asn	Ser	Val	Gln	Arg	His	Ile
	250					255					260		Ĭ.		
	Gly	His	Ala	Asn	Leu	Thr	Phe	Glu	Gln	Leu	Arg	Ser	Leu	Met	Glu
4 5	265					270					275				
	Ser	Leu	Pro	Gly	Lys	Lys	Val	Gly	Ala	Glu	Asp	Ile	Glu	Lys	Thr
	280		•			285				-	290				
5 0	Ile	Lys	Ala	Cys	Lys	Pro	Ser	Asp	Gln	Ile	Leu	Lys	Leu	Leu	Ser
.	295					300					305				
	Leu	Trp	Arg	Ile	Lys	Asn	Gly	Asp	Gln	Asp	Thr	Leu	Lys	Gly	Leu

310					315					320				
Met	His	Ala	Leu	Lys	His	Ser	Lys	Thr	Tyr	His	Phe	Pro	Lys	Thr
325					330					335				
Val	Thr	Gln	Ser	Leu	Lys	Lys	Thr	Ile	Arg	Phe	Leu	His	Ser	Phe
340					345					350			_	
Thr	Met	Tyr	Lys	Leu	Tyr	Gln	Lys	Leu	Phe	Leu	Glu	Met	Ile	Gly
355					360					365				
Asn	Gln	Val	Gln	Ser	Val	Lys	Ile	Ser	Cys	Leu				
370					375					380				

- (2) INFORMATION FOR SEQUENCE ID NO: 6:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1206

(B) TYPE : nucleic acid(C) STRANDEDNESS : single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE : cDNA (OCIF)

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 6:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240 CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300 CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360 CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420 GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480 AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540 CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600 CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660 AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720 AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780 AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC 840 GTGCAGCGGC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCGTAG CTTGATGGAA 900 AGCTTACCGG GAAAGAAAGT GGGAGCAGAA GACATTGAAA AAACAATAAA GGCATGCAAA 960 CCCAGTGACC AGATCCTGAA GCTGCTCAGT TTGTGGCGAA TAAAAAATGG CGACCAAGAC 1020

50

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ACCTTGAAGG GCCTAATGCA CGCACTAAAG CACTCAAAGA CGTACCACTT TCCCAAAACT 1080

5	GTCACTCAGA GTCTAAAGAA GACCATCAGG TATCAGAAGT TATTTTTAGA AATGATAGGT TTATAA		
10	(2) INFORMATION FOR SEQUENCE ID 1(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 15	NO: 7:	
15	(B) TYPE: amino acid(D) TOPOLOGY: linear(ii) MOLECULE TYPE: peptide (a New protein)	V-terminal amino acid s	equence of the
20	(xi) SEQUENCE DESCRIPTION :SEQ III Glu Thr Phe Pro Pro Lys Tyr Leu H 5		Ser 15
25	(2) INFORMATION FOR SEQUENCE NO I (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1185	D NO: 8:	
30	(B) TYPE : nucleic acid (C) STRANDEDNESS : single (D) TOPOLOGY : linear		
35	(ii) MOLECULE TYPE : cDNA (OCIF2) (xi) SEQUENCE DESCRIPTION :SEQ ID ATGAACAACT TGCTGTGCTG CGCGCTCGTG		GTGGACCACC 60
4 0	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TGTGACAAAT GTCCTCCTGG TACCTACCTA GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACTATACTGCA GCCCCGTGTG CAAGGAGTGC A	AAACAACACT GTACAGCAAA (ACAGACAGCT GGCACACCAG 1 AATCGCACCC ACAACCGCGT (TGGAAGACC 180 TGACGAGTGT 240 TGCGAATGC 300
45	AAGGAAGGGC GCTACCTTGA GATAGAGTTC 1 TTTGGAGTGG TGCAAGCTGG AACCCCAGAG (GGGTTCTTCT CAAATGAGAC GTCATCTAAA (CGAAATACAG TTTGCAAAAG A GCACCCTGTA GAAAACACAC A	ATGTCCAGAT 420 AATTGCAGT 480
50	GTCTTTGGTC TCCTGCTAAC TCAGAAAGGA A AACAGTGAAT CAACTCAAAA ATGTGGAATA O AGGTTTGCTG TTCCTACAAA GTTTACGCCT A CCTGGCACCA AAGTAAACGC AGAGAGTGTA O	GATGTTACCC TGTGTGAGGA G NACTGGCTTA GTGTCTTGGT A	GCATTCTTC 600 GACAATTTG 660

	GAACAGACTT TCCAGCTGCT GAAGTTATGG AAACATCAAA ACAAAGACCA AGATATAGTC	780
	AAGAAGATCA TCCAAGATAT TGACCTCTGT GAAAACAGCG TGCAGCGGCA CATTGGACAT	840
5	GCTAACCTCA CCTTCGAGCA GCTTCGTAGC TTGATGGAAA GCTTACCGGG AAAGAAAGTG	900
	GGAGCAGAAG ACATTGAAAA AACAATAAAG GCATGCAAAC CCAGTGACCA GATCCTGAAG	960
	CTGCTCAGTT TGTGGCGAAT AAAAAATGGC GACCAAGACA CCTTGAAGGG CCTAATGCAC	1020
10	GCACTAAAGC ACTCAAAGAC GTACCACTTT CCCAAAACTG TCACTCAGAG TCTAAAGAAG	1080
	ACCATCAGGT TCCTTCACAG CTTCACAATG TACAAATTGT ATCAGAAGTT ATTTTTAGAA	1140
	ATGATAGGTA ACCAGGTCCA ATCAGTAAAA ATAAGCTGCT TATAA	1185
15	(2) INFORMATION FOR SEQUENCE ID NO: 9:	
-	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 394	
20	(B) TYPE: amino acid	
20	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : protein (OCIF2)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:	
25	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser	
	-20 -15 -10	
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His	
30	-5 -1 1 5	
	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20	
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr	
05	25 30 35	
35	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His	
	40 45 50	
	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Cys	
40	55 60 65	
	Asn Arg Thr His Asn Arg Val Cys Glu Cys Lys Glu Gly Arg Tyr	
	70 75 80	
45	Leu Glu Ile Glu Phe Cys Leu Lys His Arg Ser Cys Pro Pro Gly	
	85 90. 95	
	Phe Gly Val Val Gln Ala Gly Thr Pro Glu Arg Asn Thr Val Cys	
	100 105 110	
50	Lys Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys	
	115 120 125	

	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn	Cys	Ser	Val	Phe	Gly	Leu	Leu
	130					135					140				
5	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr	His	Asp	Asn	Ile	Cys	Ser	Gly
	145					150					155			_	
		Ser	Glu	Ser	Thr		Lys	Cys	Gly	Ile		Val	Thr	Leu	Cys
10	160					165				_	170	_		6 01	_
		Glu	Ala	Phe	Phe		Phe	Ala	Val	Pro		Lys	Phe	lhr	Pro
	175	T	T	C	U - 1	180	W_1	A	.		185	C1	TL.	1	V /_ 1
1 <i>5</i>		ırp	Leu	Ser	vaı		vai	ASP	ASN	ren		GIA	inr	Lys	Val
	190	41.	Cl.	Ser	Val	195	A	Tio	I vc	A = -	200 Gln	Wic.	Sar	Sor	G1n
	205	nia	Giu	361	Val	210	ντR	116	Lys	ur R	215	1112	Set	261	GIII
	Glu	GIn	Thr	Phe	G1n		Leu	Lvs	Leu	Trn		His	Gln	Asn	Lvs
20	220	· · · ·	••••		V1	225	5 0 0	2,0	200		230				2,0
	Asp	Gln	Asp	Ile	Val		Lys	Ile	Ile	Gln		Ile	Asp	Leu	Cys
	235					240	•				245		·		•
25	Glu	Asn	Ser	Val	Gln	Arg	His	Ile	Gly	His	Ala	Asn	Leu	Thr	Phe
	250					255					260				
	Glu	G1n	Leu	Arg	Ser	Leu	Met	Glu	Ser	Leu	Pro	Gly	Lys	Lys	Val
30	265					270					275				
	Gly	Ala	Glu	Asp	Ile	Glu	Lys	Thr	Ile	Lys	Ala	Cys	Lys	Pro	Ser
	280					285					290				
25		Gln	Ile	Leu	Lys		Leu	Ser	Leu	Trp		Ile	Lys	Asn	Gly
3 5	295			_	_	300		_			305				_
		Gin	Asp	Thr	Leu		Gly	Leu	Met	His		Leu	Lys	His	Ser
	310	TL_	Т	112 -	DL -	315	T	TL	V-1	ть	320 Cl-	C	1	1	I
40	325	inr	ıyr	His	rne	330	Lys	ınr	vaı	ınr	335	Ser	Leu	Lys	Lys
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45		Leu	Phe	Leu	Glu		Ile	Glv	Asn	Gln		Gln	Ser	Val	Lvs
	355					360		,			365				_,-
		Ser	Cys	Leu											
50	370		• =	373											
50															

(2) INFORMATION FOR SEQUENCE ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 1089	
5	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
10	(ii) MOLECULE TYPE : cDNA (OCIF3)	
70	(xi) SEQUENCE DESCRIPTION ID NO: 10:	
	ATGAACAAGT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG	120
15	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC	180
	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT	240
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC	300
20	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA	360
	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA	420
	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT	480
	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA	540
25	CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC	600
	CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT	660
	AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA	720
30	AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA	780
	AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC	840
	GTGCAGCGGC ACATTGGACA TGCTAACCTC AGTTTGTGGC GAATAAAAAA TGGCGACCAA	900
	GACACCTTGA AGGGCCTAAT GCACGCACTA AAGCACTCAA AGACGTACCA CTTTCCCAAA	960
35	ACTGTCACTC AGAGTCTAAA GAAGACCATC AGGTTCCTTC ACAGCTTCAC AATGTACAAA	1020
	TTGTATCAGA AGTTATTTTT AGAAATGATA GGTAACCAGG TCCAATCAGT AAAAATAAGC	1080
	TGCTTATAA	1089
4 0		
40	(2) INFORMATION FOR SEQUENCE ID NO: 11:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 362	
45	(B) TYPE : amino acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
50	(ii) MOLECULE TYPE: protein (OCIF3)	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:	

Met Asn Lys Leu Ceu Cys Cys Ala Leu Val Phc Leu Asp Ile Ser

Ille Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His			-20)				-15	;				-10)		
Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20 Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr 25 30 35 Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His 40 45 50 Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65 Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 85 90 95 His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110 Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe Phe 115 120 125 Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn 130 135 140 Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr 145 150 165 170 Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala 175 170 Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala 175 180 185 Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val Asp 190 195 200 Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile 205 210 215 Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245		Ile			Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Туз	Lei	Hi:
10	5	_					-					•				
Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr 25			Asp	Glu	Glu	Thr		His	Gln	Leu	. Leu		Asp	Lys	Cys	Pro
25 30 35 Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His 40 45 50 Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65 Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 70 75 80 Glu Cys Lys Glu Gly Arg Tyr Leu Glu IIe Glu Phe Cys Leu Lys 85 90 95 His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110 Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe Phe 115 120 125 Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn 130 135 140 Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr 145 150 155 35 His Asp Asn IIe Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Cys 160 165 170 Gly IIe Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala 175 180 185 Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val Asp 190 195 200 Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg IIe 205 210 215 Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp IIe Val Lys Lys IIe 235 240 245			. C1v	Thr	т	Lau		C1-	u: -	C			,	-	-	~:
Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His 40	10		GIŞ	ш	1 7 1	Leu		GIU	піѕ	Cys	inr		Lys	ırp	Lys	lhi
15			Cys	Ala	Pro	Cvs		Asp	His	Tvr	Tvr		Asn	Ser	Trn	Hic
Solid Rap Office Typ Cys Ser Pro Val Cys Eys Glu Leu			•			•		•		- , -	-,-			001		
Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 70	15	Thr	Ser	Asp	Glu	Cys	Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu
70 75 80 80																
Glu Cys Lys Glu Gly Arg Tyr Leu Glu IIe Glu Phe Cys Leu Lys 85 90 95 His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110 Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe Phe 115 120 125 Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn 130 135 140 Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr 145 150 155 35 His Asp Asn IIe Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Cys 160 165 170 Gly IIe Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala 175 180 185 Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val Asp 190 195 200 Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg IIe 45 205 210 215 Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp IIe Val Lys Lys IIe 50 235 240 245			Tyr	Val	Lys	Gln	Glu	Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
85	20		_					_	_							
His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110 110 110 110 110 110 110 110			Cys	Lys	Glu	Gly		Tyr	Leu	Glu	Ile		Phe	Cys	Leu	Lys
100			Aro	Sar	Cve	Pro		Gly	Dho.	cı	V-1		C1-	41-	C1	TL
Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe Phe 115	25			001	0,3	110		dly	1 116	Gly	val		GIU	AIS	GIY	inr
115			Glu	Arg	Asn	Thr		Cys	Lys	Arg	Cys		Asp	G1v	Phe	Phe
130											•		•	•		-
Cys Ser Val Phe Gly Leu Leu Thr Gln Lys Gly Asn Ala Thr 145	30	Ser	Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn
145																
His Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Cys 160			Ser	Val	Phe	Gly		Leu	Leu	Thr	Gln		Gly	Asn	Ala	Thr
160	25		A ==	1 an	T1 -	C		C1		.	01				_	_
Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala 175			ASP	ASII	116	cys		GIY	ASN	5er	GIU		Thr	Gin	Lys	Cys
175			Ile	Asp	Vàl	Thr		Cvs	Glu	Glu	Ala		Phe	Aro	Phe	Ala
Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val Asp 190				•				-,-							1110	1114
190	40	Val	Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu		Val	Leu	Val	Asp
210 215 Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245																
Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245			Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	Arg	Ile
220 225 230 Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245	45					_										
Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245			Arg	Gln	His			Gln	Glu	Gln			Gln	Leu	Leu	Lys
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	50		ıтþ	LyS	1115			LYS	nsp	GIU			vai	LYS	Lys	He
			Gln	Asp	Ile			Cys	Glu	Asn			Gln	Arø	His	He

	250 255 260	
	Gly His Ala Asn Leu Ser Leu Trp Arg Ile Lys Asn Gly Asp Gln	
5	265 270 275	
	Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His Ser Lys Thr	
	280 285 290	
10	Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Thr Ile	
	295 300 305	
	Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys Leu	
	310 315 320	
15	Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile Ser	
	325 330 335	
	Cys Leu	
20	340 341	
	(2) INFORMATION FOR SEQUENCE ID NO: 12:	
~=	(i) SEQUENCE CHARACTERISTICS:	
25	(A) LENGTH: 465	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
30	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE : cDNA (OCIF4)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 12:	
	ATGAACAAGT TGCTGTGCTG CTCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
15	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG	120
		180
		240
o		300
	A.B. (A. (A. (A. (A. (A. (A. (A. (A. (A. (A	360
		420
	AAATTAATTA GGATCATGCA AAGTCAGATA GTTGTGACAG TTTAG	465
5		

(2) INFORMATION FOR SEQUENCE ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH :154

(B) TYPE : amino acid

	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
5	(ii) MOLECULE TYPE : protein (OCIF4)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:	
	Met Asn Lys Leu Leu Cys Cys Ser Leu Val Phe Leu Asp Ile Ser	
10	-20 -15 -0	
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His	
	-5 -1 1 5	
	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro	
15	10 15 20	
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr	
	25 30 35	
20	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His	
	40 45 50	
	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65	
25		
	Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 70 75 80	
	70 75 80 Glu Cys Lys Glu Gly Arg Tyr Leu Glu Ile Glu Phe Cys Leu Lys	
	85 90 95	
30	His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr	
	100 105 110	
	Cys Gln Cys Ala Ala Lys Leu Ile Arg Ile Met Gln Ser Gln Ile	
35	115 120 125	
	Val Val Thr Val	
	130 133	
40		
	(2) INFORMATION FOR SEQUENCE ID NO: 14:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 438	
45	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
50	(ii) MOLECULE TYPE : cDNA (OCIF5)	
	(xi) SEQUENCE DESCRIPTION ID NO: 14:	
	ATGAACAAGT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60	

	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG	
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC	120
5	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT	180
	CTATACTICA COCCOCTOTO CAACCACCTO CACTACCTOA ACCAGACALAG TGACGAGTGT	240
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC	300
	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA	360
10	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GATGCAGGAG AAGACCCAAG	420
	CCACAGATAT GTATCTGA	438
	(2) INFORMATION FOR SEQUENCE ID NO: 15:	
15	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH :140	
	(B) TYPE: amino acid	
•	(C) STRANDEDNESS : single	
20	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : protein (OCIF5)	
	(xi) SEQUENCE DESCRIPTION: ID NO: 15:	
25	Met Asn Lys Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser	
	-20 -15 -10	
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His	
30	-5 -1 1 5	
30	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro	
	10 15 20	
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr	
<i>3</i> 5	25 30 35	
	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His	
	40 45 50	
40	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu	
40	55 60 65	
	Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys	
	70 75 80	
45	Glu Cys Lys Glu Gly Arg Tyr Leu Glu Ile Glu Phe Cys Leu Lys	
	85 90 95	
	His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Cys	
	100 105 110	
50	Arg Arg Pro Lys Pro Gln Ile Cys Ile	
	115 120 124	

	(2) INFORMATION FOR SEQUENCE ID NO: 16:	
	(i) SEQUENCE CHARACTERISTICS:	
5	(A) LENGTH : 20	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
10	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer T3)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:	
	AATTAACCCT CACTAAAGGG	20
15		
	(2) INFORMATION FOR SEQUENCE ID NO: 17:	•
	(i) SEQUENCE CHARACTERISTICS:	
20	(A) LENGTH : 22	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
25	(ii) MOLECULE TYPE : synthetic DNA (primer T7)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:	•
	GTAATACGAC TCACTATAGG GC	22
30	(2) INCODUATION FOR COMPAGE TO NO. 10.	
	(2) INFORMATION FOR SEQUENCE ID NO: 18:(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
35	(B) TYPE: nucleic acid	
00	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF1)	
40	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 18:	
	ACATCAAAAC AAAGACCAAG	20
		20
45 .	(2) INFORMATION FOR SEQUENCE ID NO: 19:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	•

	<pre>(ii) MOLECULE TYPE : synthetic DNA (primer IF2) (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 19:</pre>	
5	TCTTGGTCTT TGTTTTGATG	20
	(2) INFORMATION FOR SEQUENCE ID NO: 20:	
10	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
15	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF3)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 20:	•
20	TTATTCGCCA CAAACTGAGC	20
	(2) INFORMATION FOR SEQUENCE ID NO: 21:	
	(i) SEQUENCE CHARACTERISTICS:	
25	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
30	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF4)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 21:	
35	TTGTGAAGCT GTGAAGGAAC	20
	(2) INFORMATION FOR SEQUENCE ID NO: 22:	
ю	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
5	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF5)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 22:	
o	GCTCAGTTTG TGGCGAATAA	20
	(2) INFORMATION FOR SEQUENCE ID NO: 23:	

A

	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
5	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
10	(ii) MOLECULE TYPE : synthetic DNA (primer IF6)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 23:	
	GTGGGAGCAG AAGACATTGA	20
15	(2) INFORMATION FOR SEQUENCE ID NO: 24:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
20	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF7)	
25	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 24:	•
	AATGAACAAC TTGCTGTGCT	20
	(2) INFORMATION FOR SEQUENCE ID NO: 25:	
30	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
35	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF8)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 25:	
0	TGACAAATGT CCTCCTGGTA	20
	(2) INFORMATION FOR SEQUENCE ID NO: 26:	
•	(i) SEQUENCE CHARACTERISTICS:	
9	(A) LENGTH: 20	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
,	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF9)	
	The state of the s	

	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 26:	
	AGGTAGGTAC CAGGAGGACA	20
5		
	(2) INFORMATION FOR SEQUENCE ID NO: 27:	
	(i) SEQUENCE CHARACTERISTICS:	
10	(A) LENGTH : 20	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	•
15	(ii) MOLECULE TYPE : synthetic DNA (primer IF10)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 27:	-
	GAGCTGCCCT CCTGGATTTG	20
20		
	(2) INFORMATION FOR SEQUENCE ID NO: 28:	•
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
25	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
30	(ii) MOLECULE TYPE : synthetic DNA (primer IF11)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 28:	
	CAAACTGTAT TTCGCTCTGG	20
35	(2) INFORMATION FOR SEQUENCE ID NO: 29:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
10	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF12)	
15	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 29:	
	GTGTGAGGAG GCATTCTTCA	20
·a	(2) INFORMATION FOR SEQUENCE ID NO: 30:	
U	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32	

	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS : single		
5	(D) TOPOLOGY : linear		
	(ii) MOLECULE TYPE : synthetic DNA (primer C19SF)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 30:		
10	GAATCAACTC AAAAAAGTGG AATAGATGTT AC	-	32
	(2) INFORMATION FOR SEQUENCE ID NO: 31:		
	(i) SEQUENCE CHARACTERISTICS:		
15	(A) LENGTH: 32		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS : single		
20	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE : synthetic DNA (primer C19SR)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 31:		
	GTAACATCTA TTCCACTTTT TTGAGTTGAT TC		32
25	A		
	(2) INFORMATION FOR SEQUENCE ID NO: 32:		
	(i) SEQUENCE CHARACTERISTICS:		
30	(A) LENGTH: 30		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS : single		
	(D) TOPOLOGY : linear	•	
3 5	(ii) MOLECULE TYPE : synthetic DNA (primer C20SF)		
-	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 32:		
40	ATAGATGTTA CCCTGAGTGA GGAGGCATTC		30
40			00
	(2) INFORMATION FOR SEQUENCE ID NO: 33:		
	(i) SEQUENCE CHARACTERISTICS:		
45	(A) LENGTH: 30		
	(B) TYPE : nucleic acid		
	(C) STRANDEDNESS : single		
50	(D) TOPOLOGY : linear		
30	(ii) MOLECULE TYPE : synthetic DNA (primer C20SR)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 33:		

55

-4

	GAATGCCTCC TCACTCAGGG TAACATCTAT	30
5	(2) INFORMATION FOR SEQUENCE ID NO: 34:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31	
10	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer C21SF)	
15	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 34:	
	CAAGATATTG ACCTCAGTGA AAACAGCGTG C	31
20	(2) INFORMATION FOR SEQUENCE ID NO: 35:	
20	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31	
	(B) TYPE: nucleic acid	
25	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer C21SR)	
30	(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 35:	
	GCACGCTGTT TTCACTGAGG GCAATATCTT G	31
	(2) INFORMATION FOR SEQUENCE ID NO: 36:	
35	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH : 31	
	(B) TYPE: nucleic acid	
40	(C) STRANDEDNESS : single	
•	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer C22SF)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 36:	
45	AAAACAATAA AGGCAAGCAA ACCCAGTGAC C	31
	(2) INFORMATION FOR SEQUENCE ID NO: 37:	
	(i) SEQUENCE CHARACTERISTICS:	
50	(A) LENGTH: 31	
	(B) TYPE : nucleic acid	

	(C) STRANDEDNESS : single	
_	(D) TOPOLOGY : linear	
5	(ii) MOLECULE TYPE : synthetic DNA (primer C22SR)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 37:	
	GGTCACTGGG TTTGCTTGCC TTTATTGTTT T	31
10	<u>.</u>	
	(2) INFORMATION FOR SEQUENCE ID NO: 38:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31	
15	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
20	(ii) MOLECULE TYPE: synthetic DNA (primer C23SF)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 38:	
	TCAGTAAAAA TAAGCAGCTT ATAACTGGCC A	31
25		01
25	(2) INFORMATION FOR SEQUENCE ID NO: 39:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH : 31	
30	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
25	(ii) MOLECULE TYPE : synthetic DNA (primer C23SR)	•
35	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 39:	
	TGGCCAGTTA TAAGCTGCTT ATTTTTACTG A	31
		51
40	(2) INFORMATION FOR SEQUENCE ID NO: 40:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 22	
45	(B) TYPE: nucleic acid	
₩	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF 14)	
50	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 40:	
	TTGGGGTTTA TTGGAGGAGA TG	00
	•	22

	(2) INFORMATION FOR SEQUENCE ID NO: 41:		
	(i) SEQUENCE CHARACTERISTICS:		
5	(A) LENGTH: 36		
	(B) TYPE : nucleic acid		
	(C) STRANDEDNESS : single		
10	(D) TOPOLOGY : linear	-	
	(ii) MOLECULE TYPE : synthetic DNA (primer DCR1F)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 41:		
	ACCACCCAGG AACCTTGCCC TGACCACTAC TACACA		36
15			
	(2) INFORMATION FOR SEQUENCE ID NO: 42:	* * *	
	(i) SEQUENCE CHARACTERISTICS:	•	
20	(A) LENGTH: 36		
	(B) TYPE : nucleic acid		
	(C) STRANDEDNESS : single		
	(D) TOPOLOGY : linear		
25	(ii) MOLECULE TYPE : synthetic DNA (primer DCR1R)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 42:		
	GTCAGGGCAA GGTTCCTGGG TGGTCCACTT AATGGA		36
30			
	(2) INFORMATION FOR SEQUENCE ID NO: 43:		
	(i) SEQUENCE CHARACTERISTICS:		
25	(A) LENGTH: 36	•	
35	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS : single		
	(D) TOPOLOGY : linear		
ю	(ii) MOLECULE TYPE : synthetic DNA (primer DCR2F)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 43:		
	ACCGTGTGCG CCGAATGCAA GGAAGGGCGC TACCTT		36
5	(2) INFORMATION FOR OFFICER TO US		
	(2) INFORMATION FOR SEQUENCE ID NO: 44: (i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 36		
	(B) TYPE: nucleic acid		
0			
	(C) STRANDEDNESS : single		
	(D) TOPOLOGY : linear		

	(ii) MOLECULE TYPE : synthetic DNA (primer DCR2R)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 44:	•	
5	TTCCTTGCAT TCGGCGCACA CGGTCTTCCA CTTTGC		36
	(2) INFORMATION FOR SEQUENCE ID NO: 45:		
10	(i) SEQUENCE CHARACTERISTICS:	•	
	(A) LENGTH: 36		
	(B) TYPE : nucleic acid		
	(C) STRANDEDNESS : single		
15	(D) TOPOLOGY : linear	_	
	(ii) MOLECULE TYPE : synthetic DNA (primer DCR3F)		
	(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 45:		
20	AACCGCGTGT GCAGATGTCC AGATGGGTTC TTCTCA		36
	(2) INFORMATION FOR SEQUENCE ID NO: 46:		
	(i) SEQUENCE CHARACTERISTICS:		
25	(A) LENGTH: 36		
	(B) TYPE : nucleic acid		
	(C) STRANDEDNESS : single		
30	(D) TOPOLOGY : linear		
	(ii) MOLECULE TYPE : synthetic DNA (primer DCR3R)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 46:		
	ATCTGGACAT CTGCACACGC GGTTGTGGGT GCGATT	•	36
35			
	(2) INFORMATION FOR SEQUENCE ID NO: 47:		
	(i) SEQUENCE CHARACTERISTICS:		
40	(A) LENGTH: 36		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS : single		
	(D) TOPOLOGY : linear		
45	(ii) MOLECULE TYPE : synthetic DNA (primer DCR4F)		
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 47:		
	ACAGTTTGCA AATCCGGAAA CAGTGAATCA ACTCAA		36
50	(2) INFORMATION FOR SEQUENCE ID NO: 48:		
	(i) SEQUENCE CHARACTERISTICS:		
	/-/		

	(A) LENGTH : 36 (B) TYPE : nucleic acid	
5	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer DCR4R)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 48:	
10	ACTGTTTCCG GATTTGCAAA CTGTATTTCG CTCTGG	36
	(2) INFORMATION FOR SEQUENCE ID NO: 49:	
15	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 36	
	(B) TYPE: nucleic acid	
20	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer DDD1F)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 49:	
25	AATGTGGAAT AGATATTGAC CTCTGTGAAA ACAGCG	36
	(2) INFORMATION FOR SEQUENCE ID NO: 50:	
<i>30</i>	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 36	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
35	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer DDD1R)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 50:	
40	AGAGGTCAAT ATCTATTCCA CATTTTTGAG TTGATT	36
	(2) INFORMATION FOR SEQUENCE ID NO: 51:	
	(i) SEQUENCE CHARACTERISTICS:	
4 5	(A) LENGTH : 36	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
-0	(D) TOPOLOGY : linear	•
oU.	(ii) MOLECULE TYPE : synthetic DNA (primer DDD2F)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 51:	

	AGATCATCCA AGACGCACTA AAGCACTCAA AGACGT	36
5	(2) INFORMATION FOR SEQUENCE ID NO: 52:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 36	
10	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer DDD2R)	
15	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 52:	
	GCTTTAGTGC GTCTTGGATG ATCTTCTTGA CTATAT	36
20	(2) INFORMATION FOR SEQUENCE ID NO: 53:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 29	
••	(B) TYPE : nucleic acid	
25	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer XhoI F)	
30	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 53:	
	GGCTCGAGCG CCCAGCCGCC GCCTCCAAG	29
	(2) INFORMATION FOR SEQUENCE ID NO: 54:	
35	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 20	
	(B) TYPE : nucleic acid	
40	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer IF 16)	
45	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 54:	
**	TTTGAGTGCT TTAGTGCGTG	20
	(2) INFORMATION FOR SEQUENCE ID NO: 55:	
50	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 30	
	(B) TYPE : nucleic acid	

5	(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: synthetic DNA (primer CL F) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55: TCAGTAAAAA TAAGCTAACT GGAAATGGCC	30
10		•
	(2) INFORMATION FOR SEQUENCE ID NO: 56:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30	
15	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
20	<pre>(ii) MOLECULE TYPE : synthetic DNA (primer CL R) (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 56: GGCCATTTCC AGTTAGCTTA TTTTTACTGA</pre>	30
25	(2) INFORMATION FOR SEQUENCE ID NO: 57: (i) SEQUENCE CHARACTERISTICS:	
30	(A) LENGTH: 29(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
95	(ii) MOLECULE TYPE: synthetic DNA (primer CC R) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57: CCGGATCCTC AGTGCTTTAG TGCGTGCAT	29
o	(2) INFORMATION FOR SEQUENCE ID NO: 58:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH : 29	
5	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: synthetic DNA (primer CCD2 R)	
0	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 58:	
•	CCGGATCCTC ATTGGATGAT CTTCTTGAC	29

	(2) INFORMATION FOR SEQUENCE ID NO: 59:	
	(i) SEQUENCE CHARACTERISTICS:	
5	(A) LENGTH: 29	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
10	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : synthetic DNA (primer CCD1 R)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 59:	
	CCGGATCCTC ATATTCCACA TTTTTGAGT	29
15		
	(2) INFORMATION FOR SEQUENCE ID NO: 60:	-
	(i) SEQUENCE CHARACTERISTICS:	
20	(A) LENGTH: 29	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
25	(ii) MOLECULE TYPE : synthetic DNA (primer CCR4 R)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 60:	
	CCGGATCCTC ATTTGCAAAC TGTATTTCG	29
30	(0)	
	(2) INFORMATION FOR SEQUENCE ID NO: 61:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 29	
35	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
40	(ii) MOLECULE TYPE : synthetic DNA (primer CCR3 R)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 61:	
	CCGGATCCTC ATTCGCACAC GCGGTTGTG	29
	(2) INFORMATION FOR SEQUENCE ID NO: 62:	
45	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 401	
	(B) TYPE: amino acid	
50	(C) STRANDEDNESS : single	
	(D) TOPOLOGY: linear	
	(p) for orogi - lineal	

	(ii)	MOLE	CULE	TYP	E:	Prot	ein	(OCI	F-CI	98)					
	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	ŃΟ:	62:					
5	Met	Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser
		-20					-15					-10)		
	Ile	Lys	Trp	Thr	Thr	GIn	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
10		-5				-1	1				5				
	Tyr	Asp	Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
	10					15					20				
45		Gly	Thr	Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
15	25					30					35				
		Cys	Ala	Pro	Cys	Pro	Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His
	40	_			_	45	_				50				•
20		Ser	Asp	Glu	Cys		Tyr	Cys	Ser	Pro		Cys	Lys	Glu	Leu
	55 61	.	17 1			60	_	_			65				
		Tyr	Val	Lys	Gin		Cys	Asn	Arg	Thr		Asn	Arg	Val	Cys
25	70 Glu	Cva	I vo	G1	C1	75 ^	T	1	C1	T1 -	80	DI.	~		
	85	Cys	Lys	GIU	GIA	90	ıyr	Leu	GIU	rre	95	Pne	Cys	Leu	Lys
		Arg	Ser	Cvs	Pro		G1 v	Phe	Glv	V ₂ 1		G1 _n	Ala	G1	Th.
	100		-	0,0		105	O1,	1 110	GIY	191	110	. GIII	ΛΙΔ	GIY	ш
30		Glu	Arg	Asn	Thr		Cvs	Lvs	Arg	Cvs		Asp	Glv	Phe	Phe
	115		J			120	-,-	-,-	6	-,-	125		u .,		1110
	Ser	Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys		Lys	His	Thr	Asn
35	130					135				·	140	·			
	Cys	Ser	Val	Phe	Gly	Leu	Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr
	145					150					155				
40	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu	Ser	Thr	G1n	Lys	Ser
-	160					165					170				
	Gly	Ile	Asp	Val	Thr	Leu	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
	175					180					185				
45		Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu	Ser	Val	Leu	Val	Asp
	190					195					200				
		Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	Arg	Ile
50	205					210					215				
		Arg	Gln	His			Gln	Glu	Gln	Thr	Phe	Gln	Leu	Leu	Lys
	220					225					230				

ı	Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile 235 240 245
5	Ile Gln Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile
	250 255 260 Gly His Ala Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu 265 270 275
10	Ser Leu Pro Gly Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr
15	Ile Lys Ala Cys Lys Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser 295 300 305
·	Leu Trp Arg Ile Lys Asn Gly Asp Gln Asp Thr Leu Lys Gly Leu 310 315 320
20	Met His Ala Leu Lys His Ser Lys Thr Tyr His Phe Pro Lys Thr 325 330 335
os.	Val Thr Gln Ser Leu Lys Lys Thr Ile Arg Phe Leu His Ser Phe 340 345 350
<i>25</i>	Thr Met Tyr Lys Leu Tyr Gln Lys Leu Phe Leu Glu Met Ile Gly 355 360 365
30	Asn Gln Val Gln Ser Val Lys Ile Ser Cys Leu 370 375 380
	(2) INFORMATION FOR SEQUENCE ID NO: 63: (i) SEQUENCE CHARACTERISTICS:
35	(A) LENGTH: 401 (B) TYPE: amino acid
4 0	(C) STRANDEDNESS : single (D) TOPOLOGY : linear
	(ii) MOLECULE TYPE: Protein (OCIF-C2OS) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:
4 5	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 -1 1 5
50	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr

	25					30					35				٠
	Val	Cys	s Ala	Pro	с Су:	s Pro	Ası	His	з Туз	Ty:	r Th	r As	p Se	r Tr	p His
5	40					45					50				
·	Thr	Ser	Asp	Gl:	ı Cy:	s Leu	ı Tyı	Cys	Ser	Pro	Va.	l Cy	s Lys	s Gl	u Leu
	55					60					65				
10		Tyr	· Val	Lys	Gl	ı Glu	Cys	Asn	Arg	Thr	His	s Ası	n Arg	y Va	l Cys
	70	_				75					80				
		Cys	Lys	Glu	Gly		Tyr	Leu	Glu	Ile		ı Phe	Cys	Let	ı Lys
15	85	A	C	~ -		90	61				95				
15			Ser	Cys	Pro			Phe	Gly	Val			Ala	Gly	Thr
	100 Pro		Δ-~	Acn	TL	105		I	A	C	110		01	ъ.	
	115	J1u	ıng	VSII	1111	120		LyS	ALE	cys	125		Gly	Phe	Phe
20		Asn	Glu	Thr	Ser			Ala	Pro	Cvs			Hie	Thr	Asn
	130					135	-,-			0,5	140		1113	1 111	USII
	Cys	Ser	Val	Phe	Gly		Leu	Leu	Thr	G1n			Asn	Ala	Thr
25	145					150					155				
	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu	Ser	Thr	Gln	Lys	Cys
	160					165					170				
30		Ile	Asp	Val	Thr	Leu	Ser	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
	175	_	_	_		180					185				
		Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu		Val	Leu	Val	Asp
	190	Lou	D	C1	TL	195	171			41	200				
35	205	Leu	110	GTÀ	ınr	Lys 210	val	ASN	Ala	Glu		Val	Glu	Arg	Ile
	Lys	Arg	G1n	His	Ser		Gln	G1 ₁₁	Gla	Thr	215 Pho	C1m	T	1	1
	220	•			-002	225		UIU	0111	1111	230	GIII	Leu	Leu	Lys
40	Leu	Trp	Lys	His	G1n		Lys	qzA	G1n	Asp		Val	Lvs	Lvs	Ile
	235					240	•	•			245		-,-	-,-	
	Ile	Gln	Asp	Ile	Asp	Leu	Cys	Glu	Asn	Ser	Val	Gln	Arg	His	Ile
45	250					255					260				
	Gly	His	Ala	Asn	Leu	Thr	Phe	Glu	Gln	Leu	Arg	Ser	Leu	Met	Glu
	265					270					275				
50	Ser 1	Leu	Pro	Gly			Val	Gly	Ala	Glu	Asp	Ile	Glu	Lys	Thr
50	280			_		285					290				
	Ile	Lys .	Ala	Cys	Lys	Pro	Ser	Asp	Gln	Ile	Leu	Lys	Leu	Leu	Ser

	295	300	305
_	Leu Trp Arg Ile Lys	Asn Gly Asp Gln Asp	Thr Leu Lys Gly Leu
5	310	315	320
		His Ser Lys Thr Tyr	His Phe Pro Lys Thr
	325	330	335
10		Lys Lys Thr Ile Arg	
	340	345	350
	355	Tyr Gln Lys Leu Phe 360	365
15		Val Lys Ile Ser Cys	
÷	370	375	380
20	(2) INFORMATION FOR SE	QUENCE ID NO: 64:	
	(i) SEQUENCE CHARACTER	ISTICS:	
	(A) LENGTH : 401		
	(B) TYPE: amino		
25	(C) STRANDEDNESS		
	(ii) MOUSCULE TYPE: D		
	(ii) MOLECULE TYPE : P (xi) SEQUENCE DESCRIPT		
30	Met Asn Asn Leu Leu		Pha lau Ach Ilo Son
	-20	-15	-10
	Ile Lys Trp Thr Thr	Gln Glu Thr Phe Pro I	
35	-	-1 1	5
	Tyr Asp Glu Glu Thr	Ser His Gln Leu Leu (Cys Asp Lys Cys Pro
		· ·	20
40	Pro Gly Thr Tyr Leu I		Ala Lys Trp Lys Thr
70			35
	Val Cys Ala Pro Cys I	_	
			50
45	Thr Ser Asp Glu Cys I 55		7al Cys Lys Glu Leu 85
	Gln Tyr Val Lys Gln (_	
			30
50	Glu Cys Lys Glu Gly A		
		_	95

	His 100	Arg	Ser	Cys	Pro	Pro 105		Phe	G1 y	/ Val	Va]		n Ala	Gl	y Thr
6	Pro 115	Glu	Arg	Asn	Thr	Val 120		Lys	Arg	Cys		Asp	Gly	Phe	Phe
10	Ser 130	Asn	Glu	Thr	Ser	Ser 135	Lys	Ala	Pro	Cys	Arg 140		His	Thr	: Asn
	145	Ser				150					155				
15	160	Asp .				165					170				
	175	Ile				180					185				
20	190	Pro 1				195					200				
25	205	Leu I				210					215				
20	220	Arg (•		225					230				
30	235	Trp I				240					245				
	250	Gln A His A				255					260				
35	265	Leu P				270					275		•		
	280	Lys A		٠	;	285					290				
40	295	rp Α			;	300					305				
45	310 Met H				;	315					320				
	325 Val 1					330					335				
50	340 Thr M				3	345				;	350				
	355					360		-,			365	JIU I	u c l .	116	GIÀ

	As	n Gl	n Val	l Gli	n Sei	r Va	l Ly	s Il	e Sei	r Cys	s Le	u			
	37	0				375	5				380)			
6															
	(2)	INFO	RMATI	ON F	FOR S	SEQUE	ENCE	ID I	NO: 6	35:					
	(i)	SEQUE	ENCE	CHAF	RACTE	ERIST	rics	:							
10		(A)	LENGT	H:	401									-	
		(B)	TYPE	: : a	mino	aci	id								
		(C)	STRA	NDED	NESS	; : s	ingl	e							
		(D)	TOPO	LOGY	7:1	inea	ur								
15		MOLE													
-	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q II	NO:	65:					
	Met	: Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	· Ile	Ser
eo		-20					-15					-10			
	Ιlε	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
	_	-5				-1	1				5				
<i>5</i>		Asp	Glu	Glu	Thr		His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
•	10	-01	~.	_	_	15					20				
		Gly	Thr	Tyr	Leu		Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
	25 v-1	C			_	30			_	_	35		_		
o		Cys	Ala	Pro	Cys	_	Asp	His	Tyr	Tyr		Asp	Ser	Trp	His
	40 The	San	4	C1	Coo	45	Т	C		_	50	_			
	55	Ser	ASP	GIU	Lys		ıyr	Cys	Ser	Pro		Cys	Lys	Glu	Leu
5		Tur	Val	I wa	G1-	60	C	A	A	71	65				_
	70	Tyr	141	Lys	OTII	75	Cys	ASII	Arg	inr	n1s	Asn	Arg	Val	Cys
		Cys	Lvs	Glu	Glv		Tur	I au	Gl ₁₁	Tla		Dho	C	1	1
	85	-,-	-,-		02,	90	•,,.	Deu	Olu	116	95	I He	Cys	Leu	LyS
,		Arg	Ser	Cvs	Pro		Glv	Phe	Glv	Val		GIn	Δla	Glv	Thr
	100			-,-		105	,		01 ,		110	OIII	W10	uly	1111
	Pro	Glu	Arg	Asn	Thr		Cvs	Lvs	Arg	Cvs		Asn	G1 v	Phe	Phe
;	115		_			120	•	-,-		-,-	125		01,		
	Ser	Asn	Glu	Thr	Ser		Lys	Ala	Pro	Cvs		Lvs	His	Thr	Asn
	130					135	•			-,-	140	-7-			
	Cys	Ser	Val	Phe	Gly	Leu	Leu	Leu	Thr	Gln		Gly	Asn	Ala	Thr
	1,45					150					155	,			-
	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu		Thr	Gln	Lys	Cys
							-		_	-				-,-	-,-

	160					165					170				
	Gly	Ile A	lsp'	Val	Thr	Leu	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
5	175					180					185				
	Val	Pro 1	Thr !	Lys	Phe	Thr	Pro	Asn	Trp	Leu	Ser	Val	Leu	Val	Asp
	190					195					200				
10	Asn	Leu F	ro (Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	λrg	Ile
	205					210					215				
	Lys	Arg G	ln I	His	Ser	Ser	Gln	Glu	Gln	Thr	Phe	Gln	Leu	Leu	Lys
	220					225					230				
		Trp L	ys l	lis	Gln	Asn	Lys	Asp	Gln	Asp	Ile	Val	Lys	Lys	Ile
	235					240					245				
		Gln A	sp 1	He	Asp		Cys	Glu	Asn	Ser		GIn	Arg	His	Ile
20	250	17.º - A	1 4			255	5 1			_	260	_	_		
		His A	TS A	Isn	Leu		Phe	Glu	GIn	Leu		Ser	Leu	Met	Glu
	265 Sam 1	i ou D	C	٠٦	T	270	V-1	C1	41-	C1	275	¥1.	01		4 11
25	280	Leu P	10 0	a I A	Lys	285	vaı	GIY	AIS	GIU	ASP 290	116	GIU	Lys	Inr
		Lys A	la S	ier	I.vs		Ser	Asn	C1n	Tla		Ive	Lon	ī au	Sar
	295	.,			2,3	300	561	пор	UIII	116	305		ren	Leu	Sei
		Irp A	rg I	le	Lys		G1v	Asp	Gln	Asp			Lvs	Glv	l.eu
30	310	_	-		•	315	•				320		_,_	,	-
	Met i	lis A	la L	.eu	Lys	His	Ser	Lys	Thr	Tyr	His	Phe	Pro	Lys	Thr
	325					330					335			-	٠
35	Val 1	Thr G	ln S	er	Leu	Lys	Lys	Thr	Ile	Arg	Phe	Leu	His	Ser	Phe
	340	·				345					350				
	Thr M	let T	yr L	ys :	Leu	Tyr	GIn	Lys	Leu	Phe	Leu	Glu	Met	Ile	Gly
40	355					360					365				
4.	Asn G	iln Va	al G	In :			Lys	Ile	Ser	Cys	Leu				
	370					375					380				
	/n\	CODIA	***		n	A1	an -						
4 5	(2) INF							סא ע	: 66	:					
	(i) SEQ	INCINCI	CH	AKA(CIEK	1211	₩ :								

(A) LENGTH: 401

(B) TYPE: amino acid

(C) STRANDEDNESS : single

Entertain Contraction

(D) TOPOLOGY : linear

	(ii)	MOLE	CULE	TYP	E : 1	Prot	ein	(OCI	F-C2	3S)					
5	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	NO:	66:					
•	Met	Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser
		-20					-15					-10			
	Ile	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
10		-5				-1	1				5			•	
	Tyr	Asp	Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
	10					15					20				
15		Gly	Thr	Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
	25					30					35				
		Cys	Ala	Pro	Cys		Asp	His	Tyr	Tyr		Asp	Ser	Trp	His
	40	_			_	4 5	_	_	_	_	50				_
20		Ser	Asp	Glu	Cys		Tyr	Cys	Ser	Pro		Cys	Lys	Glu	Leu
	55	•	17 1		03	60	^			æ.	65			,, ,	_
	70	Tyr	vai	Lys	GIN		Cys	Asn	Arg	inr		Asn	Arg	Val	Cys
25		Cys	Lvc	Gl.	C1 v	75	Tur	Lou	61	110	80 61	Dho	Cree	Lau	tva
	85	Cys	Lys	ara	GLY	90 AT g	1) 1	Leu	GIU	116	95	rne	Cys	Leu	Lys
		Arg	Ser	Cvs	Pro		Glv	Phe	G1 v	Vs1		Gin	41a	Glv	Thr
20	100		001	0,5		105	01,	1 110	01 ,	,	110	OII.	MIG	ulj	****
30		Glu	Arg	Asn	Thr		Cvs	Lvs	Arg	Cvs		Asp	Glv	Phe	Phe
	115		Ŭ			120	•	-,-			125		,	•	
		Asn	Glu	Thr	Ser		Lys	Ala	Pro	Cys		Lys	His	Thr	Asn
35	130					135					140				
	Cys	Ser	Val	Phe	Gly	Leu	Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr
	145					150					155				
40	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu	Ser	Thr	Gln	Lys	Cys
	160					165					170				
	Gly	Ile	Asp	Val	Thr	Leu	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
	175					180					185				
45	Val	Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu	Ser	Val	Leu	Val	Asp
	190					195					200				
		Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	Arg	Ile
50	205					210					215				
		Arg	Gln	His	Ser		Gln	Glu	Gln	Thr		Gln	Leu	Leu	Lys
	220					225					230				

	Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile
5	235 240 245
	Ile Gln Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile
	250 255 260
	Gly His Ala Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu
10	265 270 275
	Ser Leu Pro Gly Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr
	280 285 290
15	Ile Lys Ala Cys Lys Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser
	295 300 305
	Leu Trp Arg Ile Lys Asn Gly Asp Gln Asp Thr Leu Lys Gly Leu
	310 315 320
20	Met His Ala Leu Lys His Ser Lys Thr Tyr His Phe Pro Lys Thr
	325 330 335
	Val Thr Gln Ser Leu Lys Lys Thr Ile Arg Phe Leu His Ser Phe
0.5	340 345 350
25	Thr Met Tyr Lys Leu Tyr Gln Lys Leu Phe Leu Glu Met Ile Gly
	355 360 365
	Asn Gln Val Gln Ser Val Lys Ile Ser Ser Leu
30	370 375 380
	(2) INFORMATION FOR SEQUENCE ID NO: 67:
	(i) SEQUENCE CHARACTERISTICS:
35	(A) LENGTH: 360
	(B) TYPE: amino acid
	(C) STRANDEDNESS : single
40	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE: Protein (OCIF-DCR1)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 67:
	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser
45	-20 -15 -10
	Ile Lys Trp Thr Thr Gln Glu Pro Cys Pro Asp His Tyr Tyr Thr
	-5 -1 1 5
50	Asp Ser Trp His Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val
	10 15 20
	Cys Lys Glu Leu Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His

	25					30					35				
	Asn	Arg	Val	Cys	Glu	Cys	Lys	Glı	ı Gly	/ Arg		Lei	ı Gli	ı Ile	e Glu
5	40					45					50				
	Phe	Cys	Leu	Lys	His	Arg	Ser	Cys	Pro	Pro	G1 y	Phe	Gly	Va]	Val
	55					60					65				
10		Ala	Gly	Thr	Pro	Glu	Arg	Asn	Thr	Val	Cys	Lys	Arg	Ċys	Pro
	70					75					80				
		Gly	Phe	Phe	Ser		Glu	Thr	Ser	Ser		Ala	Pro	Cys	Arg
15	85	112 -	Th	4	_	90	., .	D 1			95	_			
		nıs	inr	Asn	Cys			Phe	Gly	Leu			Thr	Gln	Lys
	100 GIv	Acn	Ala	The	u; -	105		T1_	C	C	110		•		_
	115	กอก	VIG	1111	uis	120		116	Cys	Ser	125	Asn	Ser	Glu	Ser
20		Gln	Lvs	Cvs	Glv			Val	Thr	Len		Glu	Glu	Δla	Phe
	130		_•_	-,-	,	135				Dou	140	010	Olu	nia	ı u c
	Phe	Arg	Phe	Ala	Val	Pro	Thr	Lys	Phe	Thr		Asn	Trp	Leu	Ser
25	145					150					155		•		
	Val	Leu	Val	Asp	Asn	Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser
	160					165		٠			170				
30		Glu	Arg	Ile	Lys		Gln	His	Ser	Ser	Gln	Glu	Gln	Thr	Phe
	175				_	180	_				185				
	190	Leu	Leu	Lys	Leu		Lys	His	Gln	Asn		Asp	GIn	Asp	Ile
		Ive	lve	T1a	T1a	195	l an	T1.	4	T	200	01		_	., .
<i>35</i>	205	Lys	Lys	116		210	ASP	116	ASP		Cys 215	Glu	Asn	Ser	Val
		Arg	His	Ile			Ala	Asn	ī en			G1.,	Gin	I au	1
	220					225			Deu		230	oru	GIII	Leu	vr R
40	Ser	Leu	Met	Glu			Pro	Gly	Lys			Glv	Ala	Glu	Asp
	235					240		·	•	•	245	,			Пор
	Ile	Glu	Lys	Thr	Ile	Lys	Ala	Cys	Lys	Pro	Ser	Asp	Gln	Ile	Leu
45	250					255					260				
	Lys	Leu	Leu :	Ser 1	Leu	Trp	Arg	Ile	Lys	Asn	Gly	Asp	Gln	Asp	Thr
	265	_				270					275				
5 0	Leu	Lys (Gly	Leu l			Ala	Leu	Lys	His	Ser	Lys	Thr	Tyr	His
50	280 Di		, .			285 					290				
	Phe	ro l	Lys	ihr '	Val '	Thr	G1n	Ser	Leu	Lys	Lys	Thr	Ile .	Arg	Phe

	29	5				300)				30	5			
	Le	u His	s Ser	Phe	Thi	. Met	Туг	Lys	s Lei	ı Tyı	r Gli	n Lys	s Le	ı Phe	: Leu
6	310					315					320				
	Gl	u Met	t Ile	Gly	Asr	Glr	. Val	Glr	Ser	· Val	Lys	s Ile	e Sei	Cys	Leu
	329					330					338				
10														-	
	(2)	INFOR	ITAMS	ON F	OR S	EQUE	NCE	ID N	io: 6	8:					
	(i) S	SEQUE	NCE	CHAR	ACTE	RIST	ics:								
		(A)	LENG	TH:	359)									
15		(B)	TYPE	: a	mino	aci	d								
•		(C)	STRA	NDED	NESS	: s	ingl	e							
		(D)	TOP0	LOGY	: 1	inea	r								
20	(ii)	MOLE	CULE	TYP	E :	Prot	ein	(OCI	F-DC	R2)					
	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	NO:	68:					
	Met	: Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser
		-20					-15					-10			
25	Ile	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
		-5		•		-1	1				5				
	Tyr	Asp	Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
30	10					15					20				
		G1y	Thr	Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
	25	_				30					35				
		Cys	Ala	Glu	Cys	Lys	Glu	Gly	Arg	Tyr	Leu	Glu	Ile	Glu	Phe
35	40					45					50				
		Leu	Lys	His	Arg		Cys	Pro	Pro	Gly	Phe	Gly	Val	Val	Gln
	55			_		60					65				
40		Gly	Thr	Pro	Glu		Asn	Thr	Val	Cys	Lys	Arg	Cys	Pro	Asp
	70	DI	D 1	_		75		_			80				
		Phe	Phe	Ser	Asn		Thr	Ser	Ser	Lys		Pro	Cys	Arg	Lys
	85			_	_	90					95				
45		Thr	Asn	Cys			Phe	Gly	Leu	Leu	Leu	Thr	Gln	Lys	Gly
	100	4.1				105					110				
		Ala	lhr	His	Asp		Ile	Cys	Ser	Gly		Ser	Glu	Ser	Thr
50	115	1.	^	~1		120			_	_	125				
		Lys	Uys	GLY	He		Val	Thr	Leu	Cys	Glu	Glu	Ala	Phe	Phe
	130					135					140		_		
				•											

	Arg 145		Ala	Val	Pro	Thr 150		Phe	Thr	Pro	Asn 155	Trp	Leu	Ser	Val
5		Val	Asp	Asn	Leu			Thr	Lys	Val		Ala	Glu	Ser	Val
	160		_			165	·		-		170				
	Glu	Arg	Ile	Lys	Arg	Gln	His	Ser	Ser	Gln	Glu	Gln	Thr	Phe	Gln
10	175					180					185			-	
	Leu 190	Leu	Lys	Leu	Trp		His	Gln	Asn	Lys		Gln	Asp	Ile	Val
		Lys	Tle	Πe	Gln	195 Asp	Πe	Asn	l eu	Cvs	200	Acn	Sor	Va1	G1 _n
5	205				0111	210	110	пор	LÇU	0,3	215	ASII	361	141	GIII
	Arg 220	His	Ile	Gly	His	Ala 225	Asn	Leu	Thr	Phe	G1u 230	Gln	Leu	Arg	Ser
o		Met	Glu	Ser	Leu	Pro	Gly	Lys	Lys	Val	Gly	Ala	Glu	Asp	Ile
	235	•				240	_	_	_		245				
	G1u 250	Lys	Thr	Ile	Lys	Ala 255	Cys	Lys	Pro	Ser	Asp 260	Gln	Ile	Leu	Lys
5		Leu	Ser	Leu	Trp		Ile	Lys	Asn	Gly		Gln	Asp	Thr	Leu
	265					270					275		-		
		Gly	Leu	Met	His	Ala	Leu	Lys	His	Ser	Lys	Thr	Tyr	His	Phe
)	280	1	TI.	., .	mı.	285	_		_		290				_
	295	Lys	inr	val	Ihr	G1n 300	Ser	Leu	Lys		Thr 305	He	Arg	Phe	Leu
		Ser	Phe	Thr	Met		Lvs	Leu	Tvr			Leu	Phe	Leu	Glu
ī	310					315	-,-				320				
	Met	Ile	Gly	Asn	Gln	Val	Gln	Ser	Val	Lys	Ile	Ser	Cys	Leu	
	325					330					335				
1	(2) IN							D NO	: 69	:					
	(i) SE					ISTI	cs:								
		(A) L (B) T													
		(C) S													
		D) T													
	(ii) M							OCIF	-DCR	3)	-				
	(xi) S														
	Met	Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu '	Val 1	Phe 1	Leu .	Asp :	[le:	Ser

		-20					-15					-10			
5	Ile	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
5		-5				-1	1				5				
	-	Asp	Glu	Glu	Thr		His	Gln	Leu	Leu		Asp	Lys	Cys	Pro
	10			_		15			_		20		_		
10		Gly	Thr	Tyr	Leu		Gln	His	Cys	Thr		Lys	Trp	Lys	Thr
	25 V-1	C	A1 -	D	C	30	A	112 -	Т	Т	35 Th-	4	C	Т	, 17.2 -
	va1 40	Lys	Ala	rro	cys	45	ASP	nıs	ıyr	ıyr	1nr 50	ASP	Ser	irp	His
15		Sar	Asp	Glu	Cve		Tvr	Cve	Ser	Pro		Cve	Ive	C1	I eu
	55	OCI	nsp	010	0,3	60	1,1	0,3	GCI	110	65	0,3	<i>D</i> , 3	014	Leu
		Tyr	Val	Lys	Gln		Cys	Asn	Arg	Thr		Asn	Arg	Val	Cvs
20	70	·		•		75	·				80				•
	Arg	Cys	Pro	Asp	Gly	Phe	Phe	Ser	Asn	G1u	Thr	Ser	Ser	Lys	Ala
	85					90					95				
<i>2</i> 5	Pro	Cys	Arg	Lys	His	Thr	Asn	Cys	Ser	Val	Phe	Gly	Leu	Leu	Leu
25	100					105					110	_	_		
		Gln	Lys	Gly	Asn		Thr	His	Asp	Asn		Cys	Ser	Gly	Asn
	115	Glu	Sar	The	Gin	120	Cvc	G1 _w	Tla	Acn	125	Thr	Ī au	Cva	C1.,
30	130	Giu	Ser	1111	GIII	135	Cys	GIY	116	voh	140	IIII	Leu	Cys	GIU
		Ala	Phe	Phe	Arg		Ala	Val	Pro	Thr		Phe	Thr	Pro	Asn
	145	٠				150					155				
35	Trp	Leu	Ser	Val	Leu	Val	Asp	Asn	Leu	Pro	Gly	Thr	Lys	Val	Asn
	160					165					170				
	Ala	Glu	Ser	Val	Glu	Arg	Ile	Lys	Arg	GIn	His	Ser	Ser	Gln	Glu
40	175					180					185				
		Thr	Phe	Gln	Leu		Lys	Leu	Trp	Lys		Gln	Asn	Lys	Asp
	190	A	**	17 1		195	71	71.	01		200			_	6 1
45	205	Asp	Ile	vai	Lys		TIE	116	GIN	Asp		Asp	Leu	Cys	Glu
		Ser	Val	G1n	Δra	210 His	Πla	Glv	Hic	Δla	215 Asn	Lou	Thr	Pho	Glu
	220	001	,41	UIII	UTE	225	110	Uly	1113	VIG	230	Leu	IIII	1 116	GIU
50		Leu	Arg	Ser	Leu		Glu	Ser	Leu	Pro		Lys	Lys	Val	G1v
50	235		•			240					245	- • -	- • -	_	•
	Ala	Glu	Asp	Ile	Glu	Lys	Thr	Ile	Lys	Ala	Cys	Lys	Pro	Ser	Asp

	250 255 260
	Gln Ile Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys Asn Gly Asp
5	265 270 275
	Gln Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His Ser Lys
	280 285 290
10	Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Th
	295 300 305
	Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys
15	310 315 320
	Leu Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile 325 330 335
	325 330 335 Ser Cys Leu
	340
20	
	(2) INFORMATION FOR SEQUENCE ID NO: 70:
	(i) SEQUENCE CHARACTERISTICS:
25	(A) LENGTH: 359
	(B) TYPE: amino acid
	(C) STRANDEDNESS : single
30	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE : protein (OCIF-DCR4) (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 70:
	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser
35	-20 -15 -10
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His
	-5 -1 1 5
40	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro
	10 15 20
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr
	25 30 35
45	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His
	40 45 50
	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65
50	60 65 Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys
	70 75 80

	G1u 85	Cys	Lys	Glu	Gly	Arg	Tyr	Leu	Glu	Ile	Glu 95	Phe	Cys	Leu	ı Lys
5	His 100		Ser	Cys	Pro	Pro 105		Phe	Gly	Val	Val 110		Ala	Gly	Thr
	Pro		Arg	Asn	Thr		Cys	Lys	Ser	Gly			Glu	Ser	Thr
10			Cys	G1y	Ile	120 Asp	Val	Thr	Leu	Cys	125 Glu		Ala	Phe	Phe
	130					135					140				
15			Ala	Val	Pro		Lys	Phe	Thr	Pro		Trp	Leu	Ser	Val
15	145		Aan	A an	T	150 P==	C1	TL	1	V - 1	155		61	_	., .
	160		nsp	Asn	Leu	165	GIY	ınr	Lys	vai	170	Ala	GIu	Ser	Val
20			Ile	Lys	Arg		His	Ser	Ser	Gln		Gln	Thr	Phe	Gln
	175					180					185				•
		Leu	Lys	Leu	Trp		His	G1n	Asn	Lys	Asp	Gln	Asp	Ile	Val
<i>2</i> 5	190	T	T1 -	71.	C 1	195	.,			_	200		_		
	205	Lys	IIe	Ile	Gin	210	He	Asp	Leu	Cys	G1u 215	Asn	Ser	Val	Gln
		His	Ile	Gly	His		Asn	Leu	Thr	Phe		G1n	Leu	Arg	Ser
30	220					225					230			0	
		Met	Glu	Ser	Leu	Pro	Gly	Lys	Lys	Val	Gly	Ala	Glu	Asp	Ile
	235	_			_	240					245				
<i>35</i>	250	Lys	Ihr	Ile	Lys	Ala 255	Cys	Lys	Pro	Ser		Gln	Ile	Leu	Lys
		Leu	Ser	Leu	Trp		Ile	Lvs	Asn	G] v	260 Asp	Gln	Asn	Thr	Len
	265				•	270		_,_		,	275		щ		200
40	Lys	Gly	Leu	Met	His	Ala	Leu	Lys	His	Ser	Lys	Thr	Tyr	His	Phe
	280	_				285					290				
	295	Lys	Ihr	Val			Ser	Leu	Lys			Ile	Arg	Phe	Leu
45		Ser	Phe	Thr		300 Tvr	lve	Lou	T.,_		305	1	DL -	1	C1
	310			* ***		315	LJO	Leu	ıyı		320	reu	rne	ren	ara
	Met	He	Gly	Aşn	Gln	Val	GIn	Ser	Val	Lys	Ile	Ser	Cys	Leu	

(2) INFORMATION FOR SEQUENCE ID NO: 71:

	(i) S	EQUE	ENCE	CHAI	RACTE	ERIST	ICS	:							
_		(A)	LENC	STH :	326	6									
5		(B)	TYPE	: a	mino	aci	d								
		(C)	STRA	NDEI)NESS	S : s	ingl	e							
		(D)	TOPO	LOGY	: 1	inea	r					•			
10	(ii)	MOLE	CULE	TYF	E:	prot	ein	(OCI	F-DD	D1)				-	
	(xi)														
	Met			Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser
15		-20					-15					-10			
	11e		lrp	Thr	Thr		_	Thr	Phe	Pro		Lys	Tyr	Leu	His
	Tur	-5 4sn	61	C1	TL.	-1 · C	l u:-	C1-	T	ř	5			_	
20	10	nsp	Ulu	GIU	IIIL	3er 15	nis	GIU	Leu	Leu	20	Asp	Lys	Cys	Pro
20		Glv	Thr	Tvr	Leu		Gin	Hic	Cvs	Thr		Íve	Trn	ive	Thr
	25	•		-,-		30			0,0		35	2,5	пр	L)S	1111
	Val	Cys	Ala	Pro	Cys		Asp	His	Tyr	Tyr		Asp	Ser	Trp	His
25	40					45					50			-	
	Thr	Ser	Asp	Glu	Cys	Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu
	55					60					65				
30		Tyr	Val	Lys	Gln		Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
	70	•	,	41		75	_	_			80				
	61u 85	Cys	Lys	GLu	Gly		Tyr	Leu	Glu	Ile		Phe	Cys	Leu	Lys
35		Aro	Ser	Cve	Pro	90 Page	GI.	Dha	C1	V-1	95 V-1	C1	41-	C1	T1
	100	,116	Ser		110	105	GIY	rne	GIY	AST	110	GIN	A18	GIÀ	ınr
		Glu	Arg	Asn	Thr		Cvs	Lvs	Arg	Cvs		Asp	Glv	Phe	Phe
40	115					120	•	•	J	•	125		,	,	
	Ser	Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn
	130					135					140				
45		Ser	Val	Phe	Gly	Leu	Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr
45	145				±	150					155				
		Asp	Asn	Ile	Cys		Gly	Asn	Ser	Glu		Thr	G1n	Lys	Cys
	160	T1.	۸	T1	A	165	_	۵,		_	170		_		
50	Gly 175	116	usb	116			Uys	Glu	Asn	Ser		Gln	Arg	His	lle
	Gly	Hi <	Ala	Acn		180 The	Dha	G1	G1-	1	185	C	1	V - +	0 1
	,					TILL	1 116	GIU	Q TII	FAI	vr g	JUL	Leu	T9m	υIÜ

	190 195	200
		Gly Ala Glu Asp Ile Glu Lys Thr
5	205 210	215
		Asp Gln Ile Leu Lys Leu Leu Ser
	220 225	230
10	Leu Trp Arg Ile Lys Asn Gly	Asp Gln Asp Thr Leu Lys Gly Leu
	235 240	245
		Lys Thr Tyr His Phe Pro Lys Thr
15	250 255	260
75		Thr Ile Arg Phe Leu His Ser Phe
	265 270	275
	280 285	Lys Leu Phe Leu Glu Met Ile Gly
20	Asn Gln Val Gln Ser Val Lys	290 Ile Ser Cys Leu
	295 300	305
25	(2) INFORMATION FOR SEQUENCE II	O NO: 72:
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 327	
30	(B) TYPE: amino acid	
	(C) STRANDEDNESS : single	
	(b) TOPOLOGY : linear	ACTE DDDO)
35	<pre>(ii) MOLECULE TYPE : protein (0 (xi) SEQUENCE DESCRIPTION :SEQ</pre>	
		Ala Leu Val Phe Leu Asp Ile Ser
	-20 -15	-10
40	Ile Lys Trp Thr Thr Gln Glu T	Thr Phe Pro Pro Lys Tyr Leu His
40	-5 -1 1	5
	Tyr Asp Glu Glu Thr Ser His G	In Leu Leu Cys Asp Lys Cys Pro
	10 15	20
45		is Cys Thr Ala Lys Trp Lys Thr
	25 30 V-1 Co. Al B. C. B	35
	4.4	is Tyr Tyr Thr Asp Ser Trp His
50		50
	55 60	ys Ser Pro Val Cys Lys Glu Leu
		65

	G1n 70	Tyr	· Val	Lys	Gln	Glu 75	Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
5		Cys	Lys	Glu	Gly		Tyr	Leu	Glu	Ile		Phe	Cys	Leu	Lys
	His 100		Ser	Cys	Pro	Pro		Phe	Gly	Val	Val	Gln	Ala	Gly	Thr
10	Pro		Arg	Asn	Thr	Val	Cys	Lys	Arg	Cys	110 Pro	Asp	Gly	Phe	Phe
	115				_	120					125				
15	Ser 130	Asn	Glu	Thr	Ser	Ser 135	Lys	Ala	Pro	Cys	Arg 140	Lys	His	Thr	Asn
	Cys 145	Ser	Val	Phe	Gly	Leu 150	Leu	Leu	Thr	Gln	Lys 155	Gly	Asn	Ala	Thr
20		Asp	Asn	Ile	Cys		Gly	Asn	Ser	Glu		Thr	Gln	Lys	Cys
	Gly 175	Ile	Asp	Val	Thr	Leu 180	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
<i>25</i>		Pro	Thr	Lys	Phe		Pro	Asn	Trp	Leu		Val	Leu	Val	Asp
30		Leu	Pro	G1y	Thr		Val	Asn	Ala	Glu		Val	Glu	Arg	Ile
	Lys 220	Arg	GIn	His	Ser	Ser 225	G1n	Glu	Gln	Thr	Phe 230	G1n	Leu	Leu	Lys
<i>35</i>	Leu 235	Trp	Lys	His	Gln	Asn 240	Lys	Asp	Gln	Asp	Ile 245	Val	Lys	Lys	Île
	Ile 250	Gln	Asp	Aļa	Leu	Lys 255	His	Ser	Lys	Thr	Tyr 260	His	Phe	Pro	Lys
40	Thr 265	Val	Thr	G1n		Leu 270	Lys	Lys	Thr			Phe	Leu	His	Ser
		Thr	Met	Tyr	Lys		Tyr	Gln	Lys	Leu		Leu	Glu	Met	Ile
45	Gly 295	Asn	GIn	Val	GIn		Val	Lys	Ile	Ser		Leu			
(o) tw	ומחם	IATTO	N EO	n er	OUCH	OD 1	D 1/0	. 50						

- (2) INFORMATION FOR SEQUENCE ID NO: 73:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 399

		(B)	TYPE	: a	mino	aci	d								
		(C)	STRA	NDED	NESS	: s	ingl	е							
5		(D)	TOP0	LOGY	: 1	inea	r								
	(ii)	MOLE	CULE	TYP	E :	prot	ein	(OCI	F-CL)					
	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	NO:	73:					
10	Met	Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Île	Ser
		-20					-15					-10			
	Ile	Lys	Trp	Thr	Thr		Glu	Thr	Phe	Pro		Lys	Tyr	Leu	His
15	_	-5	01			-1	1			_	5		_		_
		Asp	Glu	Glu	Thr		His	GIn	Leu	Leu		Asp	Lys	Cys	Pro
	IO Pro-	C1	TL	т	T	15	C1-	112		71	20		~		
	25	Gly	IIIL	ıyr	Leu	30	GIN	nis	cys	ınr		Lys	ırp	Lys	ınr
20		Cys	Ala	Pro	Cvs		Asn	Иiс	Tvr	Tur	35 The	Δcn	Sar	Trn	Hic
	40	0,0			0,3	45	wab	1113	1,1	1,1	50	лэр	561	irp	1113
		Ser	Asp	Glu	Cvs		Tvr	Cvs	Ser	Pro		Cvs	Lvs	Glu	Leu
25	55		_		·	60	•	•			65		-,-		
	Gln	Tyr	Val	Lys	GIn	Glu	Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
	70					7 5					80				
30	Glu	Cys	Lys	Glu	Gly	Arg	Tyr	Leu	Glu	Ile	Glu	Phe	Cys	Leu	Lys
	85					90					95				
		Arg	Ser	Cys	Pro		Gly	Phe	Gly	Val	Val	Gln	Ala	Gly	Thr
35	100					105	_	_		_	110				
~		Glu	Arg	Asn	Thr		Cys	Lys	Arg	Cys		Asp	Gly	Phe	Phe
	115	Acn	C1	The	Com	120	1	A1.	D	C	125	1	17: <u>-</u>	T1	A
	130	Asn	GIU	иш	Ser	135	Lys	ита	FFO	cys	140	Lys	nis	inr	ASN
40		Ser	Val	Phe	Glv		Leu	Leu	Thr	Gin		Glv	Asn	Ala	Thr
	145				,	150	200	200	••••	· · · ·	155	U 1,	11311	MIG	1111
	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu		Thr	Gln	Lvs	Cvs
45	160					165	-				170			-•	•
	Gly	Ile	Asp	Val	Thr	Leu	Cys	Glu	Glu	Ala	Phe	Phe	Arg	Phe	Ala
	175					180					185				
50	Val	Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu	Ser	Val	Leu	Val	Asp
	190					195					200				
	Asn	Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	Arg	Ile

	205 210 215	
	Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys	
5	220 225 230	
	Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile	
	235 240 245	
10	Ile Gln Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile	
	250 255 260	
	Gly His Ala Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu	
15	265 270 275	
	Ser Leu Pro Gly Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr	
	280 285 290	
	Ile Lys Ala Cys Lys Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser 295 300 305	
20	295 300 305 Leu Trp Arg Ile Lys Asn Gly Asp Gln Asp Thr Leu Lys Gly Leu	
	310 315 320	
	Met His Ala Leu Lys His Ser Lys Thr Tyr His Phe Pro Lys Thr	
25	325 330 335	
	Val Thr Gln Ser Leu Lys Lys Thr Ile Arg Phe Leu His Ser Phe	
	340 345 350	
30	Thr Met Tyr Lys Leu Tyr Gln Lys Leu Phe Leu Glu Met Ile Gly	
	355 360 365	
	Asn Gln Val Gln Ser Val Lys Ile Ser	
25	370 375	
35	(2) INFORMATION FOR CROUDINGS IN NO. 74.	
	(2) INFORMATION FOR SEQUENCE ID NO: 74: (i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 351	
40	(B) TYPE: amino acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
45	(ii) MOLECULE TYPE: protein (OCIF-CC)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 74:	
	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser	
50	-20 -15 -10	
	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His	
	-5 -1 1 5	

	Tyr 10	Asp	Glu	Glu	Thr	Ser 15	His	Gln	Leu	Leu	Cys 20	Asp	Lys	Cys	Pro
5	Pro 25	Gly	Thr	Tyr	Leu	Lys 30	Gln	His	Cys	Thr	Ala 35	Lys	Trp	Lys	Thr
10	Val 40	Cys	Ala	Pro	Cys	Pro 45	Asp	His	Tyr	Tyr	Thr 50	Asp	Ser	Trp -	His
	Thr 55	Ser	Asp	Glu	Cys	Leu 60	Tyr	Cys	Ser	Pro	Val 65	Cys	Lys	Glu	Leu
15	Gln 70	Tyr	Val	Lys	Gln	Glu 75	Cys	Asn	Arg	Thr	His 80	Asn	Arg	Val	Cys
	Glu 85	Cys	Lys	Glu	Gly	Arg 90	Tyr	Leu	Glu	Ile	Glu 95	Phe	Cys	Leu	Lys
20	His 100	Arg	Ser	Cys	Pro	Pro 105	Gly	Phe	Gly	Val	Val 110	Gln	Ala	G1y	Thr
	Pro 115	Glu	Arg	Asn	Thr	Val 120	Cys	Lys	Arg	Cys	Pro 125	Asp	Gly	Phe	Phe
25	Ser 130	Asn	Glu	Thr	Ser	Ser 135	Lys	Ala	Pro	Cys	Arg 140	Lys	His	Thr	Asn
30	Cys 145	Ser	Val	Phe	Gly	Leu 150	Leu	Leu	Thr	Gln	Lys 155	Gly	Asn	Ala	Thr
	160					165					170		Gln		
35	175					180					185		Arg		
	190				•	195					200		Leu		
40	205					210					215		Glu	_	
•	Lys 220					225					230				•
45	Leu 235					240					245				
	250			·		255					260		Arg		
50	Gly 265	His	Ala	Asn		Thr 270	Phe	Glu	Gln		Arg 275	Ser	Leu	Met	Glu

	Ser Leu Pro Gly Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr 280 285 290
5	Ile Lys Ala Cys Lys Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser 295 300 305
10	Leu Trp Arg Ile Lys Asn Gly Asp Gln Asp Thr Leu Lys Gly Leu 310 315 320 - Met His Ala Leu Lys His
	325 330 (2) INFORMATION FOR SEQUENCE ID NO: 75:
15	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 272
20	(B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD2)
25	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 75: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10
30	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 -1 1 5 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20
35	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr 25 30 35 Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His
40	40 45 50 Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65
45	Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 70 75 80 Glu Cys Lys Glu Gly Arg Tyr Leu Glu Ile Glu Phe Cys Leu Lys 85 90 95
50	His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110
	Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe Phe 115 120 125

	Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn 130 135 140
5	Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr 145 150 155
	His Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Cys 160 165 170
10	Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg Phe Ala
	175 180 185
15	Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val Asp 190 195 200
· · · · · · · · · · · · · · · · · · ·	Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile
	205 210 215
20	Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys 220 225 230
	Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile
05	235 240 245
25	Ile Gln 250
	230
	(2) INFORMATION FOR SEQUENCE ID NO: 76:
<i>30</i>	
30	(i) SEQUENCE CHARACTERISTICS:
30	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197
30 35	(i) SEQUENCE CHARACTERISTICS:
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1)
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1)
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 -1 1 5
35 40	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro
35 40 45	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 -1 1 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20
35 40	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro
35 40 45	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 197 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: Protein (OCIF-CDD1) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76: Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -10 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -5 -1 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 20 Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr

	40					45					50				
	Thr	Ser	Asp	Glu	Cys	Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu
5	55					60					65				
		Tyr	Val	Lys	G1n		Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys
	70	C	1	C 1	61	75					80	, -	_	_	_
10	85	Lys	Lys	Glu	Gly		lyr	Leu	Glu	lle		Phe	Cys	Leu	Lys
		Ara	Ser	Cvc	Pro	90 Pro	Cl v	Dha	C1	V-1	95 V-1	C1	A1_	C1	~
	100	ıu 6	061	O, S	110	105	GIY	I He	GIY	Val	110	GIII	VIS	GIA	inr
15		Glu	Arg	Asn	Thr		Cys	Lys	Arg	Cvs		Asp	Glv	Phe	Phe
	115		_			120	•	•			125		,		
	Ser	Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys	Arg	Lys	His	Thr	Asn
20	130					135					140				
		Ser	Val	Phe	G1y		Leu	Leu	Thr	Gln	Lys	Gly	Asn	Ala	Thr
	145			.,		150					155			_	
<i>25</i>	160	Asp	Asn	He	Cys		Gly	Asn	Ser	Glu		Thr	Gln	Lys	Cys
	Gly	Tle				165					170				
	175														
30															
	(2) IN	FORM	MATIC	N FO	R SE	QUEN	ICE 1	D NO): 77	':					
	(i) SE					ISTI	cs:								
			ENGT												
35			YPE												
			TRAN OPOL	•				•							
	(ii) N							OCTE	-CCR	4)					
40	(xi) S														
			Asn								Phe	Leu	Asp	Ile	Ser
		-20					-15					-10			
45	Ile	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
	_	-5				-l	1				5				
		Asp	Glu	Glu			His	Gln	Leu			Asp	Lys (Cys	Pro
50	10 Pro	Gl	Th- '	т.,		15	C1-	บ: -	C		20 41 -	T	T		Tri
	25	GIÀ	Thr	ıyr		Lys 30	OID	nıs	Lys			Lys	ırp l	Lys	ıhr
	20					JU					35				

	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His 40 45 50
6	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu 55 60 65
10	Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys 70 75 80
	Glu Cys Lys Glu Gly Arg Tyr Leu Glu Ile Glu Phe Cys Leu Lys 85 90 95 His Arg Ser Cys Pro Pro Gly Pho Cly Vol Vol Gland Grant
15	His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala Gly Thr 100 105 110
	Pro Glu Arg Asn Thr Val Cys Lys
	115 120
20	
	(2) INFORMATION FOR SEQUENCE ID NO: 78:
	(i) SEQUENCE CHARACTERISTICS:
or	(A) LENGTH: 106
25	(B) TYPE : amino acid (C) STRANDEDNESS : single
	(D) TOPOLOGY: linear
	(ii) MOLECULE TYPE : Protein (OCIF-CCR3)
30	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 78:
	Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser
	-20 -15 -10
35	Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His
	-5 -1 1 5
	Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro
40	Pro Cly The Ten Level Co. 20
	Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr 25 30 35
	Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His
45	40 45 50
₩	Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu
	55 60 65
	Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val Cys
50	70 75 80
	Glu

5	(2) I	NFOR	[TAMS	ON F	OR S	EQUE	ENCE	ID N	10: 7	79:					
	(i) S	EQUE	NCE	CHAR	ACTE	RIST	ICS:								
		(A)	LENG	TH:	393	}									
10		(B)	TYPE	: a	mino	aci	d							•	
		(D)	TOPO	LOGY	: 1	inea	r								
	(ii)	MOLE	CULE	TYP	E :	Prot	ein	(OCI	F-CE	lst)			•		
	(xi)	SEQU	ENCE	DES	CRIP	TION	:SE	Q ID	NO:	79:					
15	Met	Asn	Asn	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Ásp	Ile	Ser
		-20	-				-15			-		-10			
	Ile	Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His
20		-5				-1	1				5				
	Tyr	Asp	Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
	10					15					20				
		Gly	Thr	Tyr	Leu		Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
25	25	_		_		30					35				
		Cys	Ala	Pro	Cys		Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His
	40				_	4 5	_	_			50				
30		Ser	Asp	Glu	Cys		Tyr	Cys	Ser	Pro		Cys	Lys	Glu	Leu
	55	Т	V_1	T	01	60	^				65				
	70	ТУГ	val	Lys	GIN		Cys	Asn	Arg	Thr		Asn	Arg	Val	Cys
		Cvc	I wa	C1	C1	75 4==	Т	1	C1	*1	80	D 1			_
35	85	cys	Lys	Glu	GIY	Arg 90	iyr	Leu	Glu	ile		Phe	Cys	Leu	Lys
		Årσ	Ser	Circ	Pro		GI.	Dha	Cl.	V ₀ 1	95 V-1	C1	A1.	C1	7"1 -
	100		OCI	Cys	110	105	OIY	rue	GIY	vai	110	GIN	M18	GIÀ	inr
o _		Glu	Arø	Asn	Thr		Cve	Ive	Ara	Cuc		Aon	C1	DL_	DL -
•	115				*****	120	cys	Lys	νιβ	Cys	125	vsh	GIY	rne	rne
	Ser	Asn	Glu	Thr	Ser		l.vs	Ala	Pro	Cve		Īve	Hic	The	A an
5	130				-01	135	۵,0		110	0,3	140	Lys	1112	ш	ASII
	Cys	Ser	Val	Phe	G1 v		Leu	Leu	Thr	G1n		Glv	Asn	Ala	Thr
	145				÷-,	150		204		U 1	155	01)	11311	VIG	1111
	His	Asp	Asn	Ile	Cys		Glv	Asn	Ser	Gĺu		Thr	G1 n	I.ve	Cve
0	160	-				165		- /	- 	- 	170		J2.1	د رت	V
	Gly	Ile	Asp	Val			Cys	Glu	Glu	Ala		Phe	Arø	Phe	Λla
			-										0	- 10	

	175	180	185									
	Val Pro Thr I	·	Asn Trp Leu Ser Val Leu Val	Acn								
5	190	195	200	nap								
	Asn Leu Pro (Gly Thr Lys Val A	Asn Ala Glu Ser Val Glu Arg	Ile								
	205	210	215									
10	Lys Arg Gln H	lis Ser Ser Gln G	Glu Gln Thr Phe Gln Leu Leu	Lys								
	220	225	230									
		lis Gln Asn Lys A	Asp Gln Asp Ile Val Lys Lys	Ile								
15	235	240	245									
			Glu Asn Ser Val Gln Arg His	Ile								
	250	255	260									
	265	sn Leu Inr Phe G 270	lu Gln Leu Arg Ser Leu Met	Glu								
20			275 Ty Ala Glu Asp Ile Glu Lys	TL								
	280	285	290	ınr								
			sp Gln Ile Leu Lys Leu Leu S	Ser								
25	295	300	305	301								
	Leu Trp Arg I	le Lys Asn Gly As	sp Gln Asp Thr Leu Lys Gly I	Leu								
	310	315	320									
30			ys Thr Tyr His Phe Pro Lys 1	hr								
	325	330	335									
	val inr Gin Se		hr Ile Arg Phe Leu His Ser F	he								
<i>35</i>		345	350									
	355	- 360	ys Leu Phe Leu Glu Met Ile G	ly								
	Asn Leu Val	. 300	365									
40	370											
70												
	(2) INFORMATION	FOR SEQUENCE ID	NO: 80:									
	(i) SEQUENCE CHA											
4 5	(A) LENGTH											
	(B) TYPE:											
		(D) TOPOLOGY: linear										
50		PE : Protein (OC										
•	(X1) SEQUENCE DE	SCRIPTION :SEQ I	D NO: 80:									

Met Asn Asn Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser

		-20)				-15	;				-10)		
	Ile	Ly:	s Trp	Thr	Thr	Gln			- Phe	Pro	Pro			Lei	ı His
5		-5				-1	1				5		- , -		
	Tyr	· Asp	Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro
	10					15					20				
10			Thr	Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr
	25					30					35				
		Cys	Ala	Pro	Cys		Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His
15	40	C		61	^	45	_	_	_	_	50				
		261	Asp	Glu	Cys		Tyr	Cys	Ser	yr Tyr Thr Asp Ser Trp His 50 er Pro Val Cys Lys Glu Leu 65 rg Thr His Asn Arg Val Cys 80 lu Ile Glu Phe Cys Leu Lys 95 ly Val Val Gln Ala Gly Thr 110 rg Cys Pro Asp Gly Phe Phe 125 ro Cys Arg Lys His Thr Asn 140 er Gln Lys Gly Asn Ala Thr					
	55 Gln	Tyr	Val	ľ vc	Cln	60	C	4	A	Tl					
	70	1 7 1	191	LJS	GIII	75	Cys	NSI1	wrg	Inr		ASN	Arg	val	Cys
20		Cys	Lys	Glu	G1v		Tvr	Leu	Glu	He		Phe	Cvs	l eu	Ive
	85	•	•		,	90	-,-					1 1.0	0,3	LCu	Lys
	His	Arg	Ser	Cys	Pro	Pro	Gly	Phe	Gly	Val		G1n	Ala	Gly	Thr
25	100					105								-	
		Glu	Arg	Asn	Thr	Val	Cys	Lys	Arg	Cys	Pro	Asp	Gly	Phe	Phe
	115					120	•								
30		Asn	Glu	Thr	Ser		Lys	Ala	Pro	Cys		Lys	His	Thr	Asn
	130	C	17 - 1	Di	41	135		_							
	145	ser	vai	Pne	Gly		Leu	Leu	Thr	Gln		Gly	Asn	Ala	Thr
<i>35</i>		Asn	Asn	Tle	Cve	150	Glv	4 cn	502	Cl.	155	TLL	C1-	T	C
	160	пор	Asn	110	U) S	165	GIY	USII	Ser	GIU	170	inr	GIN	Lys	Cys
		Ile	Asp	Vaĺ	Thr		Cvs	Glu	Glu	Ala		Phe	Aro	Phe	Ala
	175		-			180	-,-				185	1 110	6	1 110	MIA
40	Val	Pro	Thr	Lys	Phe	Thr	Pro	Asn	Trp	Leu		Val	Leu	Val	Asp
	190					195					200				•
	Asn	Leu	Pro	Gly	Thr	Lys	Val	Asn	Ala	Glu	Ser	Val	Glu	Arg	Ile
45	205					210					215				
		Arg	Gln	His			Gln	Glu	Gln	Thr	Phe	Gln	Leu	Leu	Lys
	220	T				225					230				
50	ren	ırp	Lys	His			Lys	Asp	G1n			Val	Lys	Lys	Ile
	235 Tla	G1-	A	71 -		240	_	41			245				
	115	Q T 11	Asp	тт6 .	ΛSD	∟eu ∣	UYS 1	GIU .	Asn .	Ser	Val	Gln	Arσ	His	He

	250	255	260
	Gly His Ala Asn Leu		Arg Ser Leu Met Glu
5		270	275
	Ser Leu Pro Gly Lys		Asp Ile Glu Lys Thr
		285	290
10	Ile Lys Ala Ser Leu		-
	295	300	
	(2) INFORMATION FOR SEC	QUENCE ID NO: 81:	
15	(i) SEQUENCE CHARACTER		
	(A) LENGTH: 202		
	(B) TYPE : amino a	acid	
20	(D) TOPOLOGY : lir	near	•
	(ii) MOLECULE TYPE : Pr	cotein (OCIF-CBsp)	
	(xi) SEQUENCE DESCRIPTI	ON :SEQ ID NO: 81:	
05	Met Asn Asn Leu Leu C	Cys Cys Ala Leu Val	Phe Leu Asp Ile Ser
25	-20	-15	-10
	Ile Lys Trp Thr Thr G	•	
	-5 - 10 1	_	5
30	·		20 San A. J. San San San
	Tyr Asp Glu Glu Thr S 25	_	Cys Asp Lys Cys Pro 35
	Pro Gly Thr Tyr Leu L	`	
35	40 4		od cys fir cys inc
	Val Cys Ala Pro Cys Pr		
	55 66	_	55
40	Thr Ser Asp Glu Cys Le	eu Tyr Cys Ser Pro V	al Cys Lys Glu Leu
	70 78	5 8	80
	Gln Tyr Val Lys Gln Gl	lu Cys Asn Arg Thr H	is Asn Arg Val Cys
	85 99	•	5
4 5	Glu Cys Lys Glu Gly Ar		lu Phe Cys Leu Lys
	100		10
	His Arg Ser Cys Pro Pr		
50			25
	Pro Glu Arg Asn Thr Va 130 13		
	13	. 10	40

Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn 150 :55 Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr 160 165 170 His Asp Asn Ile Cys Ser Gly 10 175 180 (2) INFORMATION FOR SEQUENCE ID NO: 82: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 84 (B) TYPE : amino acid (D) TOPOLOGY : linear 20 (ii) MOLECULE TYPE : Protein (OCIF-CPst) (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 82: Met Asn Asn Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser -20 -15 -1025 Ile Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His -1 1 Tyr Asp Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro 10 15 Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr 30 35 Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His 35 40 45 50 Thr Ser Asp Glu Cys Leu Tyr Leu Val 55 60 63 40 (2) INFORMATION FOR SEQUENCE ID NO: 83: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1206 (B) TYPE: nucleic acid (C) STRANDEDNESS : single (D) TOPOLOGY : linear (ii) MOLECULE TYPE : cDNA (OCIF-C19S) (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 83:

	ATGAACAAC	T TCCTCTCCT	CCCCCTCCT	********			
	CACCA LACC	TTCCTCCC	G CGCGCTCGTC	FITTCTGGAC	A TCTCCATTAA	GTGGACCACC	60
5	CAGGAAACG	I ITCCTCCAA	A GTACCTTCAT	TATGACGAA	G AAACCTCTCA	TCAGCTGTTC	120
	IGIGACAAA	r GTCCTCCTG(G TACCTACCTA	AAACAACACT	T GTACAGCAAA	GTGGAAGACC	180
	GTGTGCGCCC	CTTGCCCTG/	CCACTACTAC	ACAGACAGCT	GGCACACCAG	TGACGAGTGT	240
	CTATACTGCA	GCCCCGTGT(G CAAGGAGCTG	CAGTACGTCA	AGCAGGAGTG	CAATCGCACC	300
10	CACAACCGCC	TGTGCGAATO	G CAAGGAAGGG	CGCTACCTTG	AGATAGAGTT	CTGCTTGAAA	360
	CATAGGAGCT	GCCCTCCTGG	ATTTGGAGTG	GTGCAAGCTG	GAACCCCAGA	GCGAAATACA	420
	GTTTGCAAAA	GATGTCCAGA	TGGGTTCTTC	TCAAATGAGA	CGTCATCTAA	ACCACCCTCT	400
	AGAAAACACA	CAAATTGCAG	TGTCTTTGGT	CTCCTGCTAA	CTCAGAAAGG	AAATCCAACA	400
15	CACGACAACA	TATGTTCCGG	AAACAGTGAA	TCAACTCAAA	AAAGTCCAAT	ACATOTTAGO	540
	CTGTGTGAGG	AGGCATTCTT	CAGGTTTGCT	CTTCCTACAA	ACTTTACCCC	AUA I GI I ACC	600
	AGTGTCTTGG	TAGACAATTT	GCCTGGCACC	AAACTAAACC	CACACACTOR	TAACTGGCTT	660
	AAACGGCAAC	ACAGCTCACA	ACACACACT	TTCCACCTCC	CAGAGAGIGI	AGAGAGGATA	720
20	AACAAAGACC	AACATATACT	AGAACAGACT	1 TOCAGC I GC	IGAAGITATG	GAAACATCAA	780
	GTGCACCCC	ACATTCCACA	CAAGAAGATC	ATCCAAGATA	TTGACCTCTG	TGAAAACAGC	840
	ACCTTACCCC	ACATTGGACA	TGCTAACCTC	ACCITCGAGC	AGCTTCGTAG	CTTGATGGAA	900
5	AGC11ACCGG	GAAAGAAAGT	GGGAGCAGAA	GACATTGAAA	AAACAATAAA	GGCATGCAAA	960
5	CCCAGTGACC	AGATCCTGAA	GCTGCTCAGT	TTGTGGCGAA	TAAAAAATGG	CGACCAAGAC	1020
	ACCTTGAAGG	GCCTAATGCA	CGCACTAAAG	CACTCAAAGA	CGTACCACTT	TCCCAAAACT	1080
	GTCACTCAGA	GTCTAAAGAA	GACCATCAGG	TTCCTTCACA	GCTTCACAAT	GTACAAATTG	1140
)	TATCAGAAGT	TATTTTTAGA	AATGATAGGT .	AACCAGGTCC	AATCAGTAAA .	AATAAGCTGC	1200
	TTATAA						1206
							00

- (2) INFORMATION FOR SEQUENCE ID NO: 84:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1206

(B) TYPE: nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA (OCIF-C2OS)

(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 84:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240 CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300

55

40

45

CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360 CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420 GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480 AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540 CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600 CTGAGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660 AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720 AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780 AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC 840 GTGCAGCGGC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCGTAG CTTGATGGAA 900 AGCTTACCGG GAAAGAAAGT GGGAGCAGAA GACATTGAAA AAACAATAAA GGCATGCAAA 960 CCCAGTGACC AGATCCTGAA GCTGCTCAGT TTGTGGCGAA TAAAAAATGG CGACCAAGAC 1020 ACCTTGAAGG GCCTAATGCA CGCACTAAAG CACTCAAAGA CGTACCACTT TCCCAAAACT 1080 GTCACTCAGA GTCTAAAGAA GACCATCAGG TTCCTTCACA GCTTCACAAT GTACAAATTG 1140 TATCAGAAGT TATTTTTAGA AATGATAGGT AACCAGGTCC AATCAGTAAA AATAAGCTGC 1200 **TTATAA** 1206

- (2) INFORMATION FOR SEQUENCE ID NO: 85:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1206

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

- (ii) MOLECULE TYPE : cDNA (OCIF-C21S)
- (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 85:

ATGAACACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300
CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360
CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420
GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480
AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540
CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600

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CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660
AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720
AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780
AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCAG TGAAAACAGC 840
GTGCAGCGGC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCGTAG CTTGATGGAA 900
AGCTTACCGG GAAAGAAAGT GGGAGCAGAA GACATTGAAA AAACAATAAA GGCATGCAAA 960
CCCAGTGACC AGATCCTGAA GCTGCTCAGT TTGTGGCGAA TAAAAAAATGG CGACCAAGAC 1020
ACCTTGAAGG GCCTAATGCA CGCACTAAAG CACTCAAAGA CGTACCACTT TCCCAAAACT 1080
GTCACTCAGA GTCTAAAGAA GACCATCAGG TTCCTTCACA GCTTCACAAT GTACAAATTG 1140
TATCAGAAGT TATTTTAGA AATGATAGGT AACCAGGTCC AATCAGTAAA AATAAGCTGC 1200
TTATAA

- (2) INFORMATION FOR SEQUENCE ID NO: 86:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1206
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY : linear
- (ii) MOLECULE TYPE : cDNA (OCIF-C22S)
- (xi) SEQUENCE DESCRIPTION : SEQ ID NO: 86:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
CTATACTGCA GCCCCGTGTG CAAGGAGGCT CAGTACGTCA AGCAGGAGTG CAATCGCACC 300
CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360
CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420
GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480
AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540
CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600
CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660
AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720
AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780
AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC 840
GTGCAGCGCC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCCTAG CTTGATGGAA 900

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AGCTTACCGG	GAAAGAAAGT	GGGAGCAGAA	GACATTGAAA	AAACAATAAA	GGCAAGCAAA	960
CCCAGTGACC	AGATCCTGAA	GCTGCTCAGT	TTGTGGCGAA	TAAAAAATGG	CGACCAAGAC	1020
ACCTTGAAGG	GCCTAATGCA	CGCACTAAAG	CACTCAAAGA	CGTACCACTT	TCCCAAAACT	1080
GTCACTCAGA	GTCTAAAGAA	GACCATCAGG	TTCCTTCACA	GCTTCACAAT	GTACAAATTG	1140
TATCAGAAGT	TATTTTTAGA	AATGATAGGT	AACCAGGTCC	AATCAGTAAA	AATAAGCTGC	1200
TTATAA				-		1206

- (2) INFORMATION FOR SEQUENCE ID NO: 87:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1206
 - (B) TYPE : nucleic acid
 - (C) STRANDEDNESS : single
 - (D) TOPOLOGY : linear
- (ii) MOLECULE TYPE : cDNA (OCIF-C23S)
- (xi) SEQUENCE DESCRIPTION : SEQ ID NO: 87:

ATGAACAACT	TGCTGTGCTG	CGCGCTCGTG	TTTCTGGACA	TCTCCATTAA	GTGGACCACC	60
CAGGAAACGT	TTCCTCCAAA	GTACCTTCAT	TATGACGAAG	AAACCTCTCA	TCAGCTGTTG	120
TGTGACAAAT	GTCCTCCTGG	TACCTACCTA	AAACAACACT	GTACAGCAAA	GTGGAAGACC	180
GTGTGCGCCC	CTTGCCCTGA	CCACTACTAC	ACAGACAGCT	GGCACACCAG	TGACGAGTGT	240
CTATACTGCA	GCCCCGTGTG	CAAGGAGCTG	CAGTACGTCA	AGCAGGAGTG	CAATCGCACC	300
CACAACCGCG	TGTGCGAATG	CAAGGAAGGG	CGCTACCTTG	AGATAGAGTT	CTGCTTGAAA	360
CATAGGAGCT	GCCCTCCTGG	ATTTGGAGTG	GTGCAAGCTG	GAACCCCAGA	GCGAAATACA	420
GTTTGCAAAA	GATGTCCAGA	TGGGTTCTTC	TCAAATGAGA	CGTCATCTAA	AGCACCCTGT	480
AGAAAACACA	CAAATTGCAG	TGTCTTTGGT	CTCCTGCTAA	CTCAGAAAGG	AAATGCAACA	540
CACGACAACA	TATGTTCCGG	AAACAGTGAA	TCAACTCAAA	AATGTGGAAT	AGATGTTACC	600
CTGTGTGAGG	AGGCATTCTT	CAGGTTTGCT	GTTCCTACAA	AGTTTACGCC	TAACTGGCTT	660
AGTGTCTTGG	TAGACAATTT	GCCTGGCACC	AAAGTAAACG	CAGAGAGTGT	AGAGAGGATA	720
AAACGGCAAC	ACAGCTCACA	AGAACAGACT	TTCCAGCTGC	TGAAGTTATG	GAAACATCAA	780
AACAAAGACC	AAGATATAGT	CAAGAAGATC	ATCCAAGATA	TTGACCTCTG	TGAAAACAGC	840
GTGCAGCGGC	ACATTGGACA	TGCTAACCTC	ACCTTCGAGC	AGCTTCGTAG	CTTGATGGAA	900
AGCTTACCGG	GAAAGAAAGT	GGGAGCAGAA	GACATTGAAA	AAACAATAAA	GGCATGCAAA	960
CCCAGTGACC	AGATCCTGAA	GCTGCTCAGT	TTGTGGCGAA	TAAAAAATGG	CGACCAAGAC	1020
ACCTTGAAGG	GCCTAATGCA	CGCACTAAAG	CACTCAAAGA	CGTACCACTT	TCCCAAAACT	1080
GTCACTCAGA	GTCTAAAGAA	GACCATCAGG	TTCCTTCACA	GCTTCACAAT	GTACAAATTG	1140
TATCAGAAGT	TATTTTTAGA	AATGATAGGT	AACCAGGTCC	AATCAGTAAA	AATAAGCAGC	1200

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	TTATAA	1206
5	(2) INFORMATION FOR SEQUENCE ID NO: 88:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 1083	
10	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : cDNA (OCIF-DCR1)	
15	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 88:	
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
20	CAGGAACCTT GCCCTGACCA CTACTACACA GACAGCTGGC ACACCAGTGA CGAGTGTCTA	120
	TACTGCAGCC CCGTGTGCAA GGAGCTGCAG TACGTCAAGC AGGAGTGCAA TCGCACCCAC	180
	AACCGCGTGT GCGAATGCAA GGAAGGGCGC TACCTTGAGA TAGAGTTCTG CTTGAAACAT	240
	AGGAGCTGCC CTCCTGGATT TGGAGTGGTG CAAGCTGGAA CCCCAGAGCG AAATACAGTT	300
95	TGCAAAAGAT GTCCAGATGG GTTCTTCTCA AATGAGACGT CATCTAAAGC ACCCTGTAGA	360
	AAACACACAA ATTGCAGTGT CTTTGGTCTC CTGCTAACTC AGAAAGGAAA TGCAACACAC	420
	GACAACATAT GTTCCGGAAA CAGTGAATCA ACTCAAAAAT GTGGAATAGA TGTTACCCTG	480
0	TGTGAGGAGG CATTCTTCAG GTTTGCTGTT CCTACAAAGT TTACGCCTAA CTGGCTTAGT	540
-	GTCTTGGTAG ACAATTTGCC TGGCACCAAA GTAAACGCAG AGAGTGTAGA GAGGATAAAA	600
	CGGCAACACA GCTCACAAGA ACAGACTTTC CAGCTGCTGA AGTTATGGAA ACATCAAAAC	660
	AAAGACCAAG ATATAGTCAA GAAGATCATC CAAGATATTG ACCTCTGTGA AAACAGCGTG	720
5	CAGCGGCACA TTGGACATGC TAACCTCACC TTCGAGCAGC TTCGTAGCTT GATGGAAAGC	780
	TTACCGGGAA AGAAAGTGGG AGCAGAAGAC ATTGAAAAAA CAATAAAGGC ATGCAAACCC	840
	AGTGACCAGA TCCTGAAGCT GCTCAGTTTG TGGCGAATAA AAAATGGCGA CCAAGACACC	900
•	TTGAAGGGCC TAATGCACGC ACTAAAGCAC TCAAAGACGT ACCACTTTCC CAAAACTGTC	960
	ACTCAGAGTC TAAAGAAGAC CATCAGGTTC CTTCACAGCT TCACAATGTA CAAATTGTAT	1020
	CAGAAGTTAT TTTTAGAAAT GATAGGTAAC CAGGTCCAAT CAGTAAAAAT AAGCTGCTTA	1080
	TAA	1083
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	(2) INFORMATION FOR SEQUENCE ID NO: 89:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 1080	•

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(B) TYPE : nucleic acid(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA (OCIF-DCR2)

(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 89:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCG AATGCAAGGA AGGGCGCTAC CTTGAGATAG AGTTCTGCTT GAAACATAGG 240 AGCTGCCCTC CTGGATTTGG AGTGGTGCAA GCTGGAACCC CAGAGCGAAA TACAGTTTGC 300 AAAAGATGTC CAGATGGGTT CTTCTCAAAT GAGACGTCAT CTAAAGCACC CTGTAGAAAA 360 CACACAAATT GCAGTGTCTT TGGTCTCCTG CTAACTCAGA AAGGAAATGC AACACACGAC 420 AACATATGTT CCGGAAACAG TGAATCAACT CAAAAATGTG GAATAGATGT TACCCTGTGT 480 GAGGAGGCAT TCTTCAGGTT TGCTGTTCCT ACAAAGTTTA CGCCTAACTG GCTTAGTGTC 540 TTGGTAGACA ATTTGCCTGG CACCAAAGTA AACGCAGAGA GTGTAGAGAG GATAAAACGG 600 CAACACAGCT CACAAGAACA GACTTTCCAG CTGCTGAAGT TATGGAAACA TCAAAACAAA 660 GACCAAGATA TAGTCAAGAA GATCATCCAA GATATTGACC TCTGTGAAAA CAGCGTGCAG 720 CGGCACATTG GACATGCTAA CCTCACCTTC GAGCAGCTTC GTAGCTTGAT GGAAAGCTTA 780 CCGGGAAAGA AAGTGGGAGC AGAAGACATT GAAAAAACAA TAAAGGCATG CAAACCCAGT 840 GACCAGATCC TGAAGCTGCT CAGTTTGTGG CGAATAAAAA ATGGCGACCA AGACACCTTG 900 AAGGGCCTAA TGCACGCACT AAAGCACTCA AAGACGTACC ACTTTCCCAA AACTGTCACT 960 CAGAGTCTAA AGAAGACCAT CAGGTTCCTT CACAGCTTCA CAATGTACAA ATTGTATCAG 1020 AAGTTATTTT TAGAAATGAT AGGTAACCAG GTCCAATCAG TAAAAATAAG CTGCTTATAA 1080

- (2) INFORMATION FOR SEQUENCE ID NO: 90:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1092

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY : linear

- (ii) MOLECULE TYPE : cDNA (OCIF-DCR3)
- (xi) SEQUENCE DESCRIPTION : SEQ ID NO: 90:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240

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CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300 CACAACCGCG TGTGCAGATG TCCAGATGGG TTCTTCTCAA ATGAGACGTC ATCTAAAGCA 360 CCCTGTAGAA AACACACAAA TTGCAGTGTC TTTGGTCTCC TGCTAACTCA GAAAGGAAAT 420 GCAACACAC ACAACATATG TTCCGGAAAC AGTGAATCAA CTCAAAAATG TGGAATAGAT 480 GTTACCCTGT GTGAGGAGGC ATTCTTCAGG TTTGCTGTTC CTACAAAGTT TACGCCTAAC 540 TGGCTTAGTG TCTTGGTAGA CAATTTGCCT GGCACCAAAG TAAACGCAGA GAGTGTAGAG 600 AGGATAAAAC GGCAACACAG CTCACAAGAA CAGACTTTCC AGCTGCTGAA GTTATGGAAA 660 CATCAAAACA AAGACCAAGA TATAGTCAAG AAGATCATCC AAGATATTGA CCTCTGTGAA 720 AACAGCGTGC AGCGGCACAT TGGACATGCT AACCTCACCT TCGAGCAGCT TCGTAGCTTG 780 ATGGAAAGCT TACCGGGAAA GAAAGTGGGA GCAGAAGACA TTGAAAAAAC AATAAAGGCA 840 TGCAAACCCA GTGACCAGAT CCTGAAGCTG CTCAGTTTGT GGCGAATAAA AAATGGCGAC 900 CAAGACACCT TGAAGGGCCT AATGCACGCA CTAAAGCACT CAAAGACGTA CCACTTTCCC 960 AAAACTGTCA CTCAGAGTCT AAAGAAGACC ATCAGGTTCC TTCACAGCTT CACAATGTAC 1020 AAATTGTATC AGAAGTTATT TTTAGAAATG ATAGGTAACC AGGTCCAATC AGTAAAAATA 1080 AGCTGCTTAT AA 1092

- (2) INFORMATION FOR SEQUENCE ID NO: 91:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1080
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE : cDNA (OCIF-DCR4)
- (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 91:

ATGAACACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
CTATACTGCA GCCCCGTGTG CAAGGAGGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300
CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360
CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420
GTTTGCAAAT CCGGAAACAG TGAATCAACT CAAAAATGTG GAATAGATGT TACCCTGTGT 480
GAGGAGGCAT TCTTCAGGTT TGCTGTTCCT ACAAAATGTG GAATAGAGG GCTTAGTGTC 540
TTGGTAGACA ATTTGCCTGG CACCAAAGTA AACGCAGAGA GTGTAGAGAG GATAAAACGG 600
CAACACAGCT CACAAGAACA GACTTTCCAG CTGCTGAAGT TATGGAAACA TCAAAACAAA 660

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GACCAAGATA TAGTCAAGAA GATCATCCAA GATATTGACC TCTGTGAAAA CAGCGTGCAG 720
CGGCACATTG GACATGCTAA CCTCACCTTC GAGCAGCTTC GTAGCTTGAT GGAAAGCTTA 780
CCGGGAAAGA AAGTGGGAGC AGAAGACATT GAAAAAACAA TAAAGGCATG CAAACCCAGT 840
GACCAGATCC TGAAGCTGCT CAGTTTGTGG CGAATAAAAA ATGGCGACCA AGACACCTTG 900
AAGGGCCTAA TGCACGCACT AAAGCACTCA AAGACGTACC ACTTTCCCAA AACTGTCACT 960
CAGAGTCTAA AGAAGACCAT CAGGTTCCTT CACAGCTTCA CAATGTACAA ATTGTATCAG 1020
AAGTTATTTT TAGAAATGAT AGGTAACCAG GTCCAATCAG TAAAAATAAG CTGCTTATAA 1080

- (2) INFORMATION FOR SEQUENCE ID NO: 92:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 981
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS : single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE : cDNA (OCIF-DDD1)
- (xi) SEQUENCE DESCRIPTION : SEQ ID NO: 92:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240 CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300 CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360 CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420 GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480 AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540 CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATATTGAC 600 CTCTGTGAAA ACAGCGTGCA GCGGCACATT GGACATGCTA ACCTCACCTT CGAGCAGCTT 660 CGTAGCTTGA TGGAAAGCTT ACCGGGAAAG AAAGTGGGAG CAGAAGACAT TGAAAAAACA 720 ATAAAGGCAT GCAAACCCAG TGACCAGATC CTGAAGCTGC TCAGTTTGTG GCGAATAAAA 780 AATGGCGACC AAGACACCTT GAAGGGCCTA ATGCACGCAC TAAAGCACTC AAAGACGTAC 840 CACTTTCCCA AAACTGTCAC TCAGAGTCTA AAGAAGACCA TCAGGTTCCT TCACAGCTTC 900 ACAATGTACA AATTGTATCA GAAGTTATTT TTAGAAATGA TAGGTAACCA GGTCCAATCA 960 GTAAAAATAA GCTGCTTATA A 981

(2) INFORMATION FOR SEQUENCE ID NO: 93:

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(i)	SEQUENCE	CHARACTERISTICS:
` - /	CDACTION	CIRCIALO I PICTO I TOO

(A) LENGTH: 984

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA (OCIF-DDD2)

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 93:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60 CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240 CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300 CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360 CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420 GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480 AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540 CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600 CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660 AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720 AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780 AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGACG CACTAAAGCA CTCAAAGACG 840 TACCACTTTC CCAAAACTGT CACTCAGAGT CTAAAGAAGA CCATCAGGTT CCTTCACAGC 900 TTCACAATGT ACAAATTGTA TCAGAAGTTA TTTTTAGAAA TGATAGGTAA CCAGGTCCAA 960 TCAGTAAAAA TAAGCTGCTT ATAA 984

- (2) INFORMATION FOR SEQUENCE ID NO: 94:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1200
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS : single
 - (D) TOPOLOGY : linear
- (ii) MOLECULE TYPE : cDNA (OCIF-CL)
- (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 94:

ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60

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CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120 TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180 GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240 CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300 CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360 CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420 10 GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480 AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540 CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 600 15 CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660 AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720 AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780 AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC 840 20 GTGCAGCGGC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCGTAG CTTGATGGAA 900 AGCTTACCGG GAAAGAAAGT GGGAGCAGAA GACATTGAAA AAACAATAAA GGCATGCAAA 960 CCCAGTGACC AGATCCTGAA GCTGCTCAGT TTGTGGCGAA TAAAAAATGG CGACCAAGAC 1020 25 ACCTTGAAGG GCCTAATGCA CGCACTAAAG CACTCAAAGA CGTACCACTT TCCCAAAACT 1080 GTCACTCAGA GTCTAAAGAA GACCATCAGG TTCCTTCACA GCTTCACAAT GTACAAATTG 1140 TATCAGAAGT TATTTTTAGA AATGATAGGT AACCAGGTCC AATCAGTAAA AATAAGCTAA 1200

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- (2) INFORMATION FOR SEQUENCE ID NO: 95:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1056

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY : linear

- (ii) MOLECULE TYPE : cDNA (OCIF-CC)
- (xi) SEQUENCE DESCRIPTION :SEQ ID NO: 95:

ATGAACACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60

CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120

TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180

GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240

CTATACTGCA GCCCCGTGTG CAAGGAGGCT CAGTACGTCA AGCAGGAGTG CAATCGCACC 300

CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360

CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420

	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT	480
	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA	540
5	CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC	600
	CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT	
	AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA	
10	AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA	
	AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAAGATA TTGACCTCTG TGAAAACAGC	
	GTGCAGCGGC ACATTGGACA TGCTAACCTC ACCTTCGAGC AGCTTCGTAG CTTGATGGAA	-
	AGCTTACCGG GAAAGAAGT GGGAGCAGAA GACATTGAAA AAACAATAAA GGCATGCAAA	
15	CCCAGTGACC AGATCCTGAA GCTGCTCAGT TTGTGGCGAA TAAAAAATGG CGACCAAGAC	
	ACCTTGAAGG GCCTAATGCA CGCACTAAAG CACTGA	1056
20	(2) INFORMATION FOR SEQUENCE ID NO: 96:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 819	
	(B) TYPE : nucleic acid	
25	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : cDNA (OCIF-CDD2)	
30	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 96:	
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG	120
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC	
<i>3</i> 5	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT	
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC :	300
	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA;	360
40	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA	120
-	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 4	
	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA S	
	CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 6	

(2) INFORMATION FOR SEQUENCE ID NO: 97:

AACAAAGACC AAGATATAGT CAAGAAGATC ATCCAATGA

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CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660

AGTGTCTTGG TAGACAATTT GCCTGGCACC AAAGTAAACG CAGAGAGTGT AGAGAGGATA 720
AAACGGCAAC ACAGCTCACA AGAACAGACT TTCCAGCTGC TGAAGTTATG GAAACATCAA 780

	(2) INFORMATION FOR SEQUENCE ID NO: 99:	
	(i) SEQUENCE CHARACTERISTICS:	
5	(A) LENGTH: 321	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
10	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : cDNA (OCIF-CCR3)	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 99:	
15	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG	120
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC	180
20	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT	240
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC;	300
	CACAACCGCG TGTGCGAATG A	321
25	(2) INFORMATION FOR SEQUENCE ID NO: 100:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 1182	
30	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : single	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : cDNA (OCIF-CBst)	
35	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 100:	
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC	60
40	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 1	20
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 1	.80
	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 2	:4 0
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 3	100
4 5	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 3	160
	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 4	20
	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 4	80
50	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 5	40
	CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT AGATGTTACC 6	00

CTGTGTGAGG AGGCATTCTT CAGGTTTGCT GTTCCTACAA AGTTTACGCC TAACTGGCTT 660

AGTGTCTTGG	TAGACAATTT	GCCTGGCACC	AAAGTAAACG	CAGAGAGTGT	AGAGAGGATA	720
AAACGGCAAC	ACAGCTCACA	AGAACAGACT	TTCCAGCTGC	TGAAGTTATG	GAAACATCAA	780
AACAAAGACC	AAGATATAGT	CAAGAAGATC	ATCCAAGATA	TTGACCTCTG	TGAAAACAGC	840
GTGCAGCGGC	ACATTGGACA	TGCTAACCTC	ACCTTCGAGC	AGCTTCGTAG	CTTGATGGAA	900
AGCTTACCGG	GAAAGAAAGT	GGGAGCAGAA	GACATTGAAA	AAACAATAAA	GGCATGCAAA	960
CCCAGTGACC	AGATCCTGAA	GCTGCTCAGT	TTGTGGCGAA	TAAAAAATGG	CGACCAAGAC	1020
ACCTTGAAGG	GCCTAATGCA	CGCACTAAAG	CACTCAAAGA	CGTACCACTT	TCCCAAAACT	1080
GTCACTCAGA	GTCTAAAGAA	GACCATCAGG	TTCCTTCACA	GCTTCACAAT	GTACAAATTG	1140
TATCAGAAGT	TATTTTTAGA	AATGATAGGT	AACCTAGTCT	AG		1182

- (2) INFORMATION FOR SEQUENCE ID NO: 101:
- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 966

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

- (ii) MOLECULE TYPE : cDNA (OCIF-CSph)
- (xi) SEQUENCE DESCRIPTION : SEQ ID NO: 101:

ATGAACAACT	TGCTGTGCTG	CGCGCTCGTG	TTTCTGGACA	TCTCCATTAA	GTGGACCACC	60
CAGGAAACGT	TTCCTCCAAA	GTACCTTCAT	TATGACGAAG	AAACCTCTCA	TCAGCTGTTG	120
TGTGACAAAT	GTCCTCCTGG	TACCTACCTA	AAACAACACT	GTACAGCAAA	GTGGAAGACC	180
GTGTGCGCCC	CTTGCCCTGA	CCACTACTAC	ACAGACAGCT	GGCACACCAG	TGACGAGTGT	240
CTATACTGCA	GCCCCGTGTG	CAAGGAGCTG	CAGTACGTCA	AGCAGGAGTG	CAATCGCACC	300
CACAACCGCG	TGTGCGAATG	CAAGGAAGGG	CGCTACCTTG	AGATAGAGTT	CTGCTTGAAA	360
CATAGGAGCT	GCCCTCCTGG	ATTTGGAGTG	GTGCAAGCTG	GAACCCCAGA	GCGAAATACA	420
GTTTGCAAAA	GATGTCCAGA	TGGGTTCTTC	TCAAATGAGA	CGTCATCTAA	AGCACCCTGT	480
AGAAAACACA	CAAATTGCAG	TGTCTTTGGT	CTCCTGCTAA	CTCAGAAAGG	AAATGCAACA	540
CACGACAACA	TATGTTCCGG	AAACAGTGAA	TCAACTCAAA	AATGTGGAAT	AGATGTTACC	600
CTGTGTGAGG	AGGCATTCTT	CAGGTTTGCT	GTTCCTACAA	AGTTTACGCC	TAACTGGCTT	660
AGTGTCTTGG	TAGACAATTT	GCCTGGCACC	AAAGTAAACG	CAGAGAGTGT	AGAGAGGATA	720
AAACGGCAAC	ACAGCTCACA	AGAACAGACT	TTCCAGCTGC	TGAAGTTATG	GAAACATCAA	780
AACAAAGACC	AAGATATAGT	CAAGAAGATC	ATCCAAGATA	TTGACCTCTG	TGAAAACAGC	840
GTGCAGCGGC	ACATTGGACA	TGCTAACCTC	ACCTTCGAGC	AGCTTCGTAG	CTTGATGGAA	900
AGCTTACCGG	GAAAGAAAGT	GGGAGCAGAA	GACATTGAAA	AAACAATAAA	GGCTAGTCTA	960
GACTAG			•			966

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	(i) SEQUENCE CHARACTERISTICS:
5	(A) LENGTH : 594
-	(B) TYPE: nucleic acid
	(C) STRANDEDNESS : single
	(D) TOPOLOGY : linear
10	(ii) MOLECULE TYPE : cDNA (OCIF-CDD1)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 97:
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 6
15	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 12
•	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 18
	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 24
20	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 30
	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 36
	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 42
	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 48
?5	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 54
	CACGACAACA TATGTTCCGG AAACAGTGAA TCAACTCAAA AATGTGGAAT ATGA. 59
10	(2) INFORMATION FOR SEQUENCE ID NO: 98:
	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 432
	(B) TYPE : nucleic acid
5	(C) STRANDEDNESS : single
	(D) TOPOLOGY : linear
	(ii) MOLECULE TYPE : cDNA (OCIF-CCR4)
o	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 98:
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
5	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA -ACCAGGAGTG CAATCCCACC 300

CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360

CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420

432

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GTTTGCAAAT GA

(2) INFORMATION FOR SEQUENCE ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:

5	(A) LENGTH : 564
	(B) TYPE : nucleic acid
	(C) STRANDEDNESS : single
10	(D) TOPOLOGY : linear
	(ii) MOLECULE TYPE : cDNA (OCIF-CBsp)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 102:
15	
	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
20	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
	CTATACTGCA GCCCCGTGTG CAAGGAGCTG CAGTACGTCA AGCAGGAGTG CAATCGCACC 300
	CACAACCGCG TGTGCGAATG CAAGGAAGGG CGCTACCTTG AGATAGAGTT CTGCTTGAAA 360
2 5	CATAGGAGCT GCCCTCCTGG ATTTGGAGTG GTGCAAGCTG GAACCCCAGA GCGAAATACA 420
	GTTTGCAAAA GATGTCCAGA TGGGTTCTTC TCAAATGAGA CGTCATCTAA AGCACCCTGT 480
	AGAAAACACA CAAATTGCAG TGTCTTTGGT CTCCTGCTAA CTCAGAAAGG AAATGCAACA 540
30	CACGACAACA TATGTTCCGG CTAG 564
	(2) INFORMATION FOR SEQUENCE ID NO: 103:
	(i) SEQUENCE CHARACTERISTICS:
3 5	(A) LENGTH : 255
	(B) TYPE : nucleic acid
	(C) STRANDEDNESS : single
4 0	(D) TOPOLOGY : linear
	(ii) MOLECULE TYPE : cDNA (OCIF-Pst)
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 103:
45	ATGAACAACT TGCTGTGCTG CGCGCTCGTG TTTCTGGACA TCTCCATTAA GTGGACCACC 60
	CAGGAAACGT TTCCTCCAAA GTACCTTCAT TATGACGAAG AAACCTCTCA TCAGCTGTTG 120
	TGTGACAAAT GTCCTCCTGG TACCTACCTA AAACAACACT GTACAGCAAA GTGGAAGACC 180
50	GTGTGCGCCC CTTGCCCTGA CCACTACTAC ACAGACAGCT GGCACACCAG TGACGAGTGT 240
	CTATACCTAG TCTAG 255
	255
5	•

	(2) INFORMATION FOR SEQUENCE ID NO: 104:	
	(i) SEQUENCE CHARACTERISTICS:	
5	(A) LENGTH: 1317	
	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : double	
10	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE : human OCIF genomic DNA-1	
	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 104:	
15	CTGGAGACAT ATAACTTGAA CACTTGGCCC TGATGGGGAA GCAGCTCTGC AGGGACTTTT	60
	TCAGCCATCT GTAAACAATT TCAGTGGCAA CCCGCGAACT GTAATCCATG AATGGGACCA	120
	CACTITACAA GICATCAAGI CIAACTICIA GACCAGGGAA ITAAIGGGGG AGACAGCGAA	180
20	CCCTAGAGCA AAGTGCCAAA CTTCTGTCGA TAGCTTGAGG CTAGTGGAAA GACCTCGAGG	240
	AGGCTACTCC AGAAGTTCAG CGCGTAGGAA GCTCCGATAC CAATAGCCCT TTGATGATGG	300
	TGGGGTTGGT GAAGGGAACA GTGCTCCGCA AGGTTATCCC TGCCCCAGGC AGTCCAATTT	360
	TCACTCTGCA GATTCTCTCT GGCTCTAACT ACCCCAGATA ACAAGGAGTG AATGCAGAAT	420
25	AGCACGGGCT TTAGGGCCAA TCAGACATTA GTTAGAAAAA TTCCTACTAC ATGGTTTATG	480
	TAAACTTGAA GATGAATGAT TGCGAACTCC CCGAAAAGGG CTCAGACAAT GCCATGCATA	540
	AAGAGGGCC CTGTAATTTG AGGTTTCAGA ACCCGAAGTG AAGGGGTCAG GCAGCCGGGT	600
30	ACGGCGGAAA CTCACAGCTT TCGCCCAGCG AGAGGACAAA GGTCTGGGAC ACACTCCAAC	660
	TGCGTCCGGA TCTTGGCTGG ATCGGACTCT CAGGGTGGAG GAGACACAAG CACAGCAGCT	720
	GCCCAGCGTG TGCCCAGCCC TCCCACCGCT GGTCCCGGCT GCCAGGAGGC TGGCCGCTGG	780
	CGGGAAGGGG CCGGGAAACC TCAGAGCCCC GCGGAGACAG CAGCCGCCTT GTTCCTCAGC	8 40
35	CCGGTGGCTT TTTTTTCCCC TGCTCTCCCA GGGGACAGAC ACCACCGCCC CACCCCTCAC	900
	GCCCCACCTC CCTGGGGGAT CCTTTCCGCC CCAGCCCTGA AAGCGTTAAT CCTGGAGCTT	960
	TCTGCACACC CCCCGACCGC TCCCGCCCAA GCTTCCTAAA AAAGAAAGGT GCAAAGTTTG	1020
40	GTCCAGGATA GAAAAATGAC TGATCAAAGG CAGGCGATAC TTCCTGTTGC CGGGACGCTA	1080
	TATATAACGT GATGAGCGCA CGGGCTGCGG AGACGCACCG GAGCGCTCGC CCAGCCGCCG	1140
	CCTCCAAGCC CCTGAGGTTT CCGGGGACCA CA ATG AAC AAG TTG CTG TGC TGC	1193
	Met Asn Lys Leu Cys Cys	
45	-20 -15	
	GCG CTC GTG GTAAGTCCCT GGGCCAGCCG ACGGGTGCCC GGCGCCTGGG	1242
50	Ala Leu Val	
	GAGGCTGCTG CCACCTGGTC TCCCAACCTC CCAGCGGACC GGCGGGGAAA AAGGCTCCAC	1302

	TCGCTCCCTC CCAAG	1317
5	(2) INFORMATION FOR SEQUENCE ID NO: 105:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH:	
10	(B) TYPE : nucleic acid	
	(C) STRANDEDNESS : double	
	(D) TOPOLOGY : linear	
	(ii) MOLECULE TYPE: human OCIF genomic DNA-2	
15	(xi) SEQUENCE DESCRIPTION :SEQ ID NO: 105:	
	GCTTACTTTG TGCCAAATCT CATTAGGCTT AAGGTAATAC AGGACTTTGA GTCAAATGAT	@ 60
20	ACTGTTGCAC ATAAGAACAA ACCTATTTTC ATGCTAAGAT GATGCCACTG TGTTCCTTTC	120
	TCCTTCTAG TTT CTG GAC ATC TCC ATT AAG TGG ACC ACC CAG GAA ACG TTT	171
	Phe Leu Asp Ile Ser Ile Lys Trp Thr Thr Gln Glu Thr Phe	
	-10 -5 -1 1	
2 5		
	CCT CCA AAG TAC CTT CAT TAT GAC GAA GAA ACC TCT CAT CAG CTG TTG	219
	Pro Pro Lys Tyr Leu His Tyr Asp Glu Glu Thr Ser His Gln Leu Leu	
30	5 10 15	
	TGT GAC AAA TGT CCT CCT GGT ACC TAC CTA AAA CAA CAC TGT ACA GCA	267
	Cys Asp Lys Cys Pro Pro Gly Thr Tyr Leu Lys Gln His Cys Thr Ala	
35	20 25 30 35	
	AAG TGG AAG ACC GTG TGC GCC CCT TGC CCT GAC CAC TAC TAC ACA GAC	315
10	Lys Trp Lys Thr Val Cys Ala Pro Cys Pro Asp His Tyr Tyr Thr Asp	
	40 45 50	
	AGC TGG CAC ACC AGT GAC GAG TGT CTA TAC TGC AGC CCC GTG TGC AAG	363
15	Ser Trp His Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro Val Cys Lys	
	55 60 65	
'n	GAG CTG CAG TAC GTC AAG CAG GAG TGC AAT CGC ACC CAC AAC CGC GTG	411
•	Glu Leu Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His Asn Arg Val	
	70 75 80	
	•	

	TGC GAA TGC AAG GAA GGG CGC TAC CTT GAG ATA GAG TTC TGC TTG AAA	459
	Cys Glu Cys Lys Glu Gly Arg Tyr Leu Glu Ile Glu Phe Cys Leu Lys	
5	85 90 95	
	CAT AGG AGC TGC CCT CGT GGA TTT GGA GTG GTG CAA GCT G GTACGTGTCA	509
10	His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala	
	100 105 110	
	ATGTGCAGCA AAATTAATTA GGATCATGCA AAGTCAGATA GTTGTGACAG TTTAGGAGAA	569
15	CACTTTTGTT CTGATGACAT TATAGGATAG CAAATTGCAA AGGTAATGAA ACCTGCCAGG	629
	TAGGTACTAT GTGTCTGGAG TGCTTCCAAA GGACCATTGC TCAGAGGAAT ACTTTGCCAC	689
	TACAGGGCAA TTTAATGACA AATCTCAAAT GCAGCAAATT ATTCTCTCAT GAGATGCATG	749
20	ATGGTTTTTT TTTTTTTTT TAAAGAAACA AACTCAAGTT GCACTATTGA TAGTTGATCT	809
	ATACCTCTAT ATTTCACTTC AGCATGGACA CCTTCAAACT GCAGCACTTT TTGACAAACA	869
	TCAGAAATGT TAATTTATAC CAAGAGAGTA ATTATGCTCA TATTAATGAG ACTCTGGAGT	929
	GCTAACAATA AGCAGTTATA ATTAATTATG TAAAAAATGA GAATGGTGAG GGGAATTGCA	989
25	TTTCATTATT AAAAACAAGG CTAGTTCTTC CTTTAGCATG GGAGCTGAGT GTTTGGGAGG	1049
	GTAAGGACTA TAGCAGAATC TCTTCAATGA GCTTATTCTT TATCTTAGAC AAAACAGATT	1109
•	GTCAAGCCAA GAGCAAGCAC TTGCCTATAA ACCAAGTGCT TTCTCTTTTG CATTTTGAAC	1169
30	AGCATTGGTC AGGGCTCATG TGTATTGAAT CTTTTAAACC AGTAACCCAC GTTTTTTTTC	1229
	TGCCACATTT GCGAAGCTTC AGTGCAGCCT ATAACTTTTC ATAGCTTGAG AAAATTAAGA	1289
	GTATCCACTT ACTTAGATGG AAGAAGTAAT CAGTATAGAT TCTGATGACT CAGTTTGAAG	1349
	CAGTGTTTCT CAACTGAAGC CCTGCTGATA TTTTAAGAAA TATCTGGATT CCTAGGCTGG	1409
35	ACTCCTTTTT GTGGGCAGCT GTCCTGCGCA TTGTAGAATT TTGGCAGCAC CCCTGGACTC	1469
	TAGCCACTAG ATACCAATAG CAGTCCTTCC CCCATGTGAC AGCCAAAAAT GTCTTCAGAC	1529
	ACTGTCAAAT GTCGCCAGGT GGCAAAATCA CTCCTGGTTG AGAACAGGGT CATCAATGCT	1589
40	AAGTATCTGT AACTATTTTA ACTCTCAAAA CTTGTGATAT ACAAAGTCTA AATTATTAGA	1649
	CGACCAATAC TTTAGGTTTA AAGGCATACA AATGAAACAT TCAAAAATCA AAATCTATTC	1709
	TGTTTCTCAA ATAGTGAATC TTATAAAATT AATCACAGAA GATGCAAATT GCATCAGAGT	1769
	CCCTTAAAAT TCCTCTTCGT ATGAGTATTT GAGGGAGGAA TTGGTGATAG TTCCTACTTT	1829
4 5	CTATTGGATG GTACTTTGAG ACTCAAAAGC TAAGCTAAGT TGTGTGTGTG TCAGGGTGCG	1889
	GGGTGTGGAA TCCCATCAGA TAAAAGCAAA TCCATGTAAT TCATTCAGTA AGTTGTATAT	1949
	GTAGAAAAAT GAAAAGTGGG CTATGCAGCT TGGAAACTAG AGAATTTTGA AAAATAATGG	2009
50	AAATCACAAG GATCTTTCTT AAATAAGTAA GAAAATCTGT TTGTAGAATG AAGCAAGCAG	2069
	GCAGCCAGAA GACTCAGAAC AAAAGTACAC ATTTTACTCT GTGTACACTG GCAGCACAGT	2129
	GGGATTTATT TACCTCTCCC TCCCTAAAAA CCCACACAGC GGTTCCTCTT GGGAAATAAG	2189

AGGITTCCAG CCCAAAGAGA AGGAAAGACT ATGIGGTGIT ACTCTAAAAA GTATITAATA ACCGITITGI TGITGCTGIT GCTGITTTGA AATCAGATTG TCTCCTCC ATATITTATT TACTTCATIC TGITAATTCC TGIGGAATTA CTTAGACCAA GCATGGTGAA TTCTCAACTG TAAAGCCAAA TTTCTCCATC ATATATATTC CACATTITGC CTGGCAGGIT ATAATTTTA TATTTCCACT GATAGTAATA AGGTAAAATC ATTACTTAGA TGGATAGACT TTATTCATAA AAAGTACCAT CAGTTATAGA GGGAAAGTCA TGTCATCTTC AGGAAGGTCA TTAGATAAAG CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATTCTTTT GTTAAATAAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCT ATAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGAATGA ACAAGATTCT TAGGCCCGGC ACGCCAGGCACA GATATGTATC TGAAGAGTA ACAAGATTCT TAGGCCCGGC ACGCCAGGCA CCCTGCACCA ATGAGAACA CCCCCCTCTA CTAAAAATTAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGG ATGAGACTCC GTCACACCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGG ATGAGACTCC GCACCCCCGC CCCCCCCCCC			
TACTICATTC IGTTAATTCC IGTGGAATTA CITAGAGCAA GCATGGTGAA TITCTCAACTG TAAAGCCAAA TITCTCCATC ATTATAATTT CACATTTTGC CTGGCAGGTT ATAATTTTA TATTTCCACT GATAGTAATA AGGTAAAATC ATTACTTAGA TGGATAGATC TITTTCATAA AAAGTACCAT CAGTTATAGA GGGAAGTCAT GTTCATGTTC AGGAAGGTCA TTAGATAAAG CTTCTGAATA TATTAGAAA CATTAGTTCT GTCATTCTTA GATTCTTTT GTTAAATAAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCT ATTAGGATGGC AGGAGAAGAC CCAAGCCACA GATAGTTCT TGAAGAATA ACAGGCTGGCC ACGCCTGCA GCTCAGCCAGA TCAAGAATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGATGA ACAGGCGGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCCACA ATGATGAACAC CCTGCCTCTA CTAACAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCCG CCCCCCCC CTTCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC CTCCAGCCTG CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCCG CCCCCCCCC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGCT ACTTATTTCG AGAAACTAAC GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGCTG ACTTATTTCG AGAAACTAAC CAACAAAACA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AAGGTGTAGT AGGAAAATA CTCAGTGCAA TGCTGGAAACA AAAACCCTC TTTGCTTTGT AAGGTGTGT CTAAGAAATA TGCAGTGCAA TGCTGGAAACA AAAACCCTC TTTTGCTTTGT AAGGTGTTC CTAAGAAATA TGCAGTGCAA TGCTGGAAACT AAAATTTAA ATGTGAAGGT AAGGTGTAT AGGAAAATA GTCAGTGCAA TGCTGGAAAT AAAATTTAA ATGTGAAGGT TTTAGGCTGG GTTTTCCCCC CCTGTTCTTT TTTTCTCCCA GCCCTTTGCC ATTTTTGCAG GTCAATGAAA CATGTAGAAA GAGACAGGGA ATGAACTAG AACCAGTCCA TTTTGCCCCT TTTTTATTTTTTTTTTTTTTTTTTTTTTT			2249
TACHICATIC IGHAATICE IGIGGATTIA CITAGACCAA GCATGGTGAA TTCTCAACTG TAAAGCCAAA TTTCTCATC ATTATAATTI CACATTTIGC CTGGCAGGTT ATAATTTTTA TATTTCCACT GATAGTAATA AGGTAAAATC ATTACTTAGA TGGAAGGTCA TTTACATAAG TATTCCACT CAGTTATAGA GGGAAGTCAT GTTCATGTTC AGGAAGGTCA TTAGATAAAG CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATCTTTTT GTTAAATAAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGCAATA ACAGCATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGC AAGGCCGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCCTCA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAG AGGCTGAGAC CTCCAGCCTG GGTGACACAG ATGACACTC GTCCCTCCAG CCTCCAGCCC CTCCAGCCCG CTCCAGCCAG GTGAACCATAC GCAGCACAA AAGAATATC CTCAAGAATTA CAAAAATTAGC AGGGCATGGT GGTGACACAG GTTGTGGTGA GCTGAGACC CTCCAGCCTG GGTGACACAGA ATGACACTCC GTCCCTGCCG CCCCCCCC CTTCCCCCCC AAAAAACTTC TTCTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGCT ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCATGGA ATCCCTGCCC AAAAACCCTC GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTTAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAAACA GAAAACCCTC TTTTGCCCCT CTTTTTTTTTT		ACCGTTTTGT TGTTGCTGTT GCTGTTTTGA AATCAGATTG TCTCCTCTCC	2309
TATTTCCACT GATAGTAATA AGGTAAAATC ATTACTTAGA TGGATAGATC TTTTTCATAA AAAGTACCAT CAGTTATAGA GGGAAGTCAT GTTCATGTTC AGGAAGGTCA TTAGATAAAG CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATTCTTTT GTTAAATAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGATGA ACAGATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAAGAGTC AAAGCCGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGCCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCTGCCG CCGCCCCCCCC AAAAAGATTC CTTGAACCCT CAGGCCGGAG GTTGTGGTGA GCTGAGATCC CTCTCACTCAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCTGCCG CCGCCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGGC TGCCAACTC ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCATGGA ATCCCTGCCC AAATACCTC GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTAGTGCAC AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCCTGGAAT AATATTTAAT ATGTGAAGGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCCTGGAAAT AATATTTAAT ATGTGAAGGT TTTTTTATTT TCTGGTTTTG CTAAAAACAAA CACACAAACA GAAAACCCTC TTTTGCTTTGT TTTTTTATTT TCTGGTTTTG CTAAAAACAAA CACACAAACA GAAACCCTC TTTTGCCCCT TTTTTTATTT TCTGGTTTTG CTAAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT ACCTTTCATT TTTCTCTTC ATATTTGTA TCTTGCCCCT TTTTTAATTA AAGTTTCTG AAAAACAAA CAATCAGGAATAGA ACCAGTCCA TTTTGCCCCT TTTACACTAGA TGCAGATAAT TTCATATTCA GATATTCAAA TATTTTTCAA TCTGGCATCAC GTAAATAGT CAAGTGTTTG AGGTTTTCAAA TTTTTAAAAA TATTTTTCAA TATTTTTCAA AAATGCCCTT GCAGTCACCC TTCCTGAATT TTTTAATCAAA TATTTTTCAA TATTTTTCAA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTTAACAATA TATTTTTCAA TATTTTTCAA AAATGCCCTT GCAGTCACCC TTCCTGAATT TTGAACCACT CTCCTGTTTT AAACAGATT AAAAGGCCTTA TATCATCTT CCGTTTACTA TGTGACCACT CTCCTGTTTT AAACAGATT AAAAGGCCTTAATATT TCCATTTATTA TATTAATAAA TATTTTTCAA AATTTTTTCAA AAATGCCCTT CACACCACA ACGTTTACTA TGTAACCACTAAT TTCAAGAGAT CTCAGCGGCC AACTTTATTT TCCTTTCAA AA	5	TACTTCATTC TGTTAATTCC TGTGGAATTA CTTAGAGCAA GCATGGTGAA TTCTCAACTG	2369
AAAGTACCAT CAGTTATAGA GGGAAGTCAT GTTCATGTTC AGGAAGGTCA TTAGATAAAG CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATTCTTTT GTTAAATAAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGATGA ACAAGATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGTC AAGGCCGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCTGCCG CCGCCCCCGC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGCGTCCAGG TGTCCAAGTC ACTTATTTCG AGTAAATTAG CAATCAAAGA ATGCCATGGA ATCCCTGCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGTAAATTAG CAATCAAAGA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTCCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT CTTATGATA TGTAAAACAAA CACACAAACA GAAAACCCTC TTTTCCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGTC ATTTTTGCACT TTTTTTATTT TCTGGTTTTG GTAAAAACAAA CAACAAACAG GAACACCTC TTTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGCGTGAG ATTTATAAAAT GAAGTTTAAT AAGTTTCTGT AGCCTTGATT TTTTCTTTCTTTC ATATTTTGTTA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTTTTTTTT		TAAAGCCAAA TTTCTCCATC ATTATAATTT CACATTTTGC CTGGCAGGTT ATAATTTTTA	2429
CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATTCTTTT GTTAAATAAC TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGAATGA ACAAGATTCT TAGGCCGGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGTC AAGGCGGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCC CCGCCCCCGC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCTGCAACA AAGGGAGAC TGCTCCAGGC TGTCCAAGCT ACTTATTTCG AGAACATACG GCAGTCACA AAGGGAGAC TGCGTCCAGG TGTCCAAGTC ACTTATTTCG AGAACATACG GCAGTCACA AAGGGAGAC TGCGTCCAGG TGTCCAAGTC ACTTATTTCG AGAAAATTA TGATATACAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCCT TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAA AAAACCCCT TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AAATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTT TTTTCTGCCA GCCCTTTGCC ATTTTGCAG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTTTTTTTT TCTGGTTTTG GTAAAACAAA CAACAACAA AACCAGTCCA TTTTGCCCCT TTTTTTTTTTT TCTGGTTTTG GTAAAAGAAA CAACAGGAGA AACCAGTCCA TTTTGCCCCT TTTTTTTTTTT TCTGGTTTTG GTAAAAGAAA CAACAGGAGA AACCAGTCCA TTTTGCCCCT TTTTTTTTTTT TCTGGTTTTG GTAAAAGAAA CAACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTATTT TCTGGTTTTG GTAAAAGAAA CAACAGGAGA ACCAGTCCA TTTTGCCCCT TTTTATTT TCTGGTTTTG GTAAAAGAAA CAACAGGAGA AACCAGTCCA TTTTGCCCCT TTTTATTTT TCTGGTTTTG GTAAAAGAAA CAACAGGAGA AACCAGTCCA TTTTGCCCCT TTTTATTTT TCTGGTTTTG GTAAAATTCA CAATTAGAG TCTAAAATCTG TTCAAATCTG GAAGTTTAAA AAGTTTCTGT AGCTTTGATT TTTCTTTTC ATATTTGAA TCTGTAAATCTG TTCAAACTAGC TTCAAGGTT CAAGGATATT TTCAATTTCA GATACACTGG AATGTATGT CTAGCCATGC GTAATATAGC CAAGTACTT TCCATCAAA TATTTTTCAA TATTTTTTCA TCTAGGACTGA AAATGCCTT CAAGCACCA GAGTATCT TGAACCTTAA CTCAGGAAA GAAAGACTT CAGGCAGAACA AACCACCA GAGTTACTA TGAAGCATA TTTCAAGAATA AATCCCTTTTCA AACCACCA GAGTTACTT TGAAGCTTAA TAATGTTTAA AACCACTTAC TCCAAGGAT AACCAGCCTT ACCCCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTCAA AATGCCTTAA CACCACCAC		TATTTCCACT GATAGTAATA AGGTAAAATC ATTACTTAGA TGGATAGATC TTTTTCATAA	2489
TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGAATGA ACAAGATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAAGAGTC AAGGCGGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCC CCGCCCCCCC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGAACATACG GCAGTCAACA AAGGGAGCC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTAGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGATAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTGCTTTGT AAGGTGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT AGGATGATAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGAAA CAACAAACAA GAGGCTCCA TTTTGCCCCT TTTTTTTTTTTTT TCTGGTTTTG GTAAAAGATA CAATGAAGTA GAGCGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCACATATG GATATTGAAG TCTAAATCTG TTCAACTAGC TTACACTAGA TGGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTG AAGGTATTA TTTTTTAATA CTTTGCACTAGC TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTTTTAAA TCTTGGACTGC GTAATATAGT CAAGTGTTG AAGGTATTA TTTTTTAATA CTCTTTGCTTTTAAATCTG TCTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTTAATA CTCTTTTGCTTTTAAATCTG TCTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTTAATAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACCTGG AATGTATGAT CTAGCCATGC GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGGTTTAT TAATGTTGTA AATTTTTAACA AAATGCCCTT CCGAGTCACCC TTCCTGAAGT TTGAACCTG ATTTTTTAATATA TAATGTTGTA AATTTTTAATCAT AAGGATTA TTCAAAGAAT TTCAAACAAT GGAATAATTT TAATGATGC AGCATTATTA TAATGTTGTA AATTTTTAACGCACT CACAATTAGG ATTCAAGGAAA GAAAGAACTT CAGGAGAACACA GCACACACA GAGTTTACT TGAGCTTAA TGAGGAAA AATTTTTAATGATCT CACAATTAGG ATTCAATGG ATTCAAGAAAAAACCCCCTACC CTTCTTTCCT TC	10	AAAGTACCAT CAGTTATAGA GGGAAGTCAT GTTCATGTTC AGGAAGGTCA TTAGATAAAG	2549
AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGAATGA ACAAGATTCT TAGGCCCGGC ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGTC AAGGCGGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC CTCCAGCCTG GGTGACAGGA ATGAGACTCC GTCCCTGCCG CCTCCAGGCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGAC CTCCAGCCCG AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGAC TGGGTCCAGG TGTCCAAGCTC ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCCATGGA ATCCCTGCCC AAAAACCCTCT GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAACAAA CACACAAACA GACGCCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCCCCTT CATTTTTTCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTTGTA TCTTGCATAA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGATGAT CTAGCCATGC GTAATATAGT CAAGGTTTT AAGGTATTA TTTTTAAAAC CGTCTTTTTT TCAACCTAGC TTCAAGGTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TCCTGTACTA TTGAACCACT CTCCTGTTTT AAACCAGTCA AAATGCCCTT GCAGTCACCC TCCTGTACTA TGTAACCTTAC TCCCCGCGCTT ACGCTTTTGA GTCAAGGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTTAA AATTTTTACA AAATGCCCTT GCAGTCACCC TCCTGTTACTA TGTAACCACT CTCCTGTTTT AAACCAGTA AATTTTTACAC GAGTACCT GCGTTTACTA TGTAACCACT CTCCTGTTTTA AAACCAGTTA AATTTTTACAC GTCAAGGAC AACTTTATTG CACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACA GTCAAGGAC ACCTTACTA GGAGTTACT TGATCTAAT GGAATAATTG TATGAAGAAT CCACTACCACC CACCTTCCAA AAGTTTATTA TAATGTTGTA TATCAAGAAT TTCAAAGAAT ATGCCTGCAA ACACCCCTACC AGCGTTACTA TGACCTACC GGACTAATGA ACACCCTACC CTTCTTTCCT TCCCTCC		CTTCTGAATA TATTATGAAA CATTAGTTCT GTCATTCTTA GATTCTTTTT GTTAAATAAC	2609
ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGTC AAGGCGGGCA GATCACCTGA GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC AGGAGAATCT CTTGAACCCT CGAGGCGGAG GTTGTGGTGA GCTGAGATCC CTCTACTGCA CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCCG CCGCCCCCGC CTTCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG AGGATGTAGT AGGAAAGTAC TAAAAACCAAA CACACAAACA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTATGATA TTGTAGAATT TGATAATAGAG TTGTATCCCA TTTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACCAAA CACACAAACA GAAAACCCTC TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTCACA GCCCTTTGCC ATTTTGCAGG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACCAG ACCAGTCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GAGCGTTGAA ATTTTAAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTC ATATTTGTA TCTTGCATAA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTTTCT ATATTTGTA TCTTGCATAA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTTCAACTAGC TTCAAACTGC TTACACTAGA TGGAGATATT TCATATTCA GATACCTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTA TTTTTAATAG CTCTTTAAGCTTG GTAAATATGT CAAGTGTTTG AAGGTATTA TTTTTAATAA TATTTTCCA TCAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTA TTTTTAATAA TATTTTTCCA TCAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTA TTTTTAATAG CTCTTTGGACTTG AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACCAGTTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACCAGTTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACCAGTTA AAATGCCTT GCAGTACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACCAGTTA AAATGCATATAGG CAACACACA GCAGTTACT TGAATTTAT TAATGTTGTA AATTTTTACT CAGCAGAAGG ACACACA GCAGTTACT TGATTTTATA GGAATAATTG TATGAAGAAT GCATATTACAC CAGACACACA GCAGTTACT TGATTTTCTA GGAATAATTG TATGAAGAAT CAGCTGGAA ACACCGGCCTT ACTGCCACTC AGCGGGGGGGT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCCAC ATTTCATGAG CGTTTTGTAG GGAATAATTG ACACCCTACC CTTCTTTCCT TTCCTCCAC ATTTCATGAG CGTTTT		TTTAAAAGCT AACTTACCTA AAAGAAATAT CTGACACATA TGAACTTCTC ATTAGGATGC	2669
GGTCAGGAGT TCAAGACCAG CCTGGCCAAC ATGATGAAC CCTGCCTCTA CTAAAAATAC AAAAATTAGC AGGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC AGGAGAATCT CTTGAACCCT CGAGGCGGAG GTTGTGTGTGA GCTGAGATCC CTCTACTGCA CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCCTGCCG CCGCCCCCGC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGAC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTATGATA TTGTAGAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGTC ATTTTTGCAG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTTGCAG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GAAGTTTAAT AAGTTTCTG AGCTTTGATT TTTTCTCTTTC ATATTTGTTA TCTTGCATAA GAAGTTTAAT AAGTTTCTG AGCTTTTATT AGAACCAGG ATGTAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACCTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAAAAT TATGTGTAGT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAAAAT TATTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACCAGC CTGCTGTTTT AAACCAGTTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACCAGC CTGCTGTTTT AAACCAGTTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACCAGC CTGCTGTTTT AAACCAGTTA AGCAAATGGT AATCATCTT CCGTTTACTA TGTAGCCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCCAA AAGTTTATTA TAATGTTGTA AATTTTTACT CCGTAGGGAC TGATGGAAT TTAATGATGC AGCATTCAAT GGGAATAATTG TATGAAGAAT GTCAGCGGCC ACCTTTATTG GCACCTTCCAA AAGTTTATTA TAATGTTGTA AATTTTTACT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGAATAATTG TATGAAGAAT GATATTACAG CAGACACAC GCAGTTACTT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGCCTT ACTGCCACCT ACGCGTTTTGTA GGAATAATTG TATGAAGAAT ATGGCTGAA ACACCGGCCTT ACTGCCACCT ACG		AGGAGAAGAC CCAAGCCACA GATATGTATC TGAAGAATGA ACAAGATTCT TAGGCCCGGC	2729
AAAAATTAGC AGGCATGGT GGTGCATGCC TGCAACCCTA GCTACTCAGG AGGCTGAGAC AGGAGAATCT CTTGAACCCT CGAGGCGGAG GTTGTGGTGA GCTGAGATCC CTCTACTGCA CTCCAGCCTG GGTGACAGAG ATGAGACTCC GTCCTGCCG CCGCCCCCGC CTTCCCCCCC AAAAAGATTC TTCTTCATGC AGAACATACG GCAGTCAACA AAGGGAGACC TGGGTCCAGG TGTCCAAGTC ACTTATTTCG AGTAAATTAG CAATGAAAGA ATGCCATGGA ATCCCTGCCC AAATACCTCT GCTTATGATA TTGTAGAAATT TGATATAGAG TTGTATCCCA TTTAAGGAGT AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCCT TTTGCTTTGT AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT TTTAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGCT ATTTTTGCAG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTAAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCCTTTC ATATTTGTTA TCTTGCATAA GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAAATCTG TTCAACTAGC TTACACTAGA TGGAGGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAAG CTCTAAAATCTG TTCAACTAGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAAG CTCTATATTTCCA TCATGGAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACCTGG AATGTATGAT CTAGGCCTGG TTCAAGGTTT TCTGCCAATG ATTTCTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGGTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCCTTAA CTGCCAGGCT ACGCTTTTGA GCAGAATGGT ATATCATCTT CCGTTTACTA TGTAGCCTTAA CTGCCAGGCT ACGCTTTTGA GCAGAATGGT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAAGGAA AATTTTACT CAGTAGGAC TGATTGGAAT TTAATGATC AGCATTCAAT GGAGTAATTA TATCAAGAAT GATATTACAC CAGACACACA GCAGTTATCT TGATTTTTCA GGAATAATTG TATGAAGAAT GATATTACAC CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT GATATTACAC CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT GATATTACAC CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGAC ACACGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCCAC ATTTCATGAG CGTTTTTGTAG GTAACCAGAA AATTGACTTG	15	ACGGTGGCTC ACATCTGTAA TCTCAAGAGT TTGAGAGGTC AAGGCGGGCA GATCACCTGA	2789
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TITAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGTC ATTTTTGCAG GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT 45 TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACCAGAA AATTGACTTGC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTTGTAG GTAACCAGAA AATTGACTTGC		AGGATGTAGT AGGAAAGTAC TAAAAACAAA CACACAAACA GAAAACCCTC TTTGCTTTGT	3269
GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA 35 GCCAGAATTG GCCTGTAAAA TCTACATATG GATACACTGG AATGTATGAT CTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT 45 TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATTG ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACCAGAA AATTGACTTG		AAGGTGGTTC CTAAGATAAT GTCAGTGCAA TGCTGGAAAT AATATTTAAT ATGTGAAGGT	3329
TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCTACATATG GATACACTGG ACTGAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT 45 TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG	30	TITAGGCTGT GTTTTCCCCT CCTGTTCTTT TTTTCTGCCA GCCCTTTGTC ATTTTTGCAG	3389
GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGGCT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT 45 TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		GTCAATGAAT CATGTAGAAA GAGACAGGAG ATGAAACTAG AACCAGTCCA TTTTGCCCCT	3449
GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAATCTG TTCAACTAGC TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACCAGAA AATTGACTTG		TTTTTTATTT TCTGGTTTTG GTAAAAGATA CAATGAGGTA GGAGGTTGAG ATTTATAAAT	3509
TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACCAGAA AATTGACTTG		GAAGTTTAAT AAGTTTCTGT AGCTTTGATT TTTCTCTTTC ATATTTGTTA TCTTGCATAA	3569
GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT 45 TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG	35	GCCAGAATTG GCCTGTAAAA TCTACATATG GATATTGAAG TCTAAATCTG TTCAACTAGC	3629
TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		TTACACTAGA TGGAGATATT TTCATATTCA GATACACTGG AATGTATGAT CTAGCCATGC	3689
AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		GTAATATAGT CAAGTGTTTG AAGGTATTTA TTTTTAATAG CGTCTTTAGT TGTGGACTGG	3749
AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG	40	TTCAAGTTTT TCTGCCAATG ATTTCTTCAA ATTTATCAAA TATTTTTCCA TCATGAAGTA	3809
GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		AAATGCCCTT GCAGTCACCC TTCCTGAAGT TTGAACGACT CTGCTGTTTT AAACAGTTTA	3869
TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		AGCAAATGGT ATATCATCTT CCGTTTACTA TGTAGCTTAA CTGCAGGCTT ACGCTTTTGA	3929
CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		GTCAGCGGCC AACTTTATTG CCACCTTCAA AAGTTTATTA TAATGTTGTA AATTTTTACT	3989
GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT ATGGCTGACA ACACCGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG	1 5	TCTCAAGGTT AGCATACTTA GGAGTTGCTT CACAATTAGG ATTCAGGAAA GAAAGAACTT	4049
ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		CAGTAGGAAC TGATTGGAAT TTAATGATGC AGCATTCAAT GGGTACTAAT TTCAAAGAAT	4109
CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG		GATATTACAG CAGACACACA GCAGTTATCT TGATTTTCTA GGAATAATTG TATGAAGAAT	4169
CTTCTTTCCT TTCCTCTCAC ATTTCATGAG CGTTTTGTAG GTAACGAGAA AATTGACTTG	50	ATGGCTGACA ACACGGCCTT ACTGCCACTC AGCGGAGGCT GGACTAATGA ACACCCTACC	4229
	50		4289
			4349

GAGAAGGTAC TAAATTGCTT GGTATTTTCC GTAG GA ACC CCA GAG CGA Gly Thr Pro Glu Arg 115 10 GTT TGC AAA AGA TGT CCA GAT GGG TTC TTC TCA AAT GAG ACG Val Cys Lys Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr 120 125 130 AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145 CTA ACT CAG AAA GGA AAA GGA AAT GCA ACA CAC GAC AAC ATA TGT TCC	A AAT ACA 4523 R Asn Thr TCA TCT 4571 Ser Ser 135 CTC CTG 4619
GTT TGC AAA AGA TGT CCA GAT GGG TTC TTC TCA AAT GAG ACG Val Cys Lys Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr 120 125 130 AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	Ser Ser 135 CTC CTG 4619 Leu Leu
GTT TGC AAA AGA TGT CCA GAT GGG TTC TTC TCA AAT GAG ACG Val Cys Lys Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr 120 125 130 AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	Ser Ser 135 CTC CTG 4619 Leu Leu
120 125 130 AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	135 CTC CTG 4619 Leu Leu
AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	CTC CTG 4619 Leu Leu
AAA GCA CCC TGT AGA AAA CAC ACA AAT TGC AGT GTC TTT GGT Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	Leu Leu
Lys Ala Pro Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly 140 145	Leu Leu
20 140 145	
20	150
CTA ACT CAG AAA GGA AAT GCA ACA CAC GAC AAC ATA TGT TCC	100
CIA ACI CAU AAA GUA AAI GAA ACA CAC GAC AAC AIA 11-1 11.C	204 440
Leu Thr Gln Lys Gly Asn Ala Thr His Asp Asn Ile Cys Ser	
25 155 160 165	GIY ASN
100	
AGT GAA TCA ACT CAA AAA TGT GGA ATA G GTAATTACAT TCCAAAA	TAC 4715
Ser Glu Ser Thr Gln Lys Cys Gly Ile	
170 175	
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	TCGGATGCA 5555

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	CACTAGACTA ATCTCAGACC TTCACTCAAA GACACATTAC ACTAAAGATG ATTTGCTTTT	5675
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	TACTATGTGG TACTGTGCTA TAGAGGCTTT AACATTTATA AAAACACTGT GAAAGTTGCT	6035
	TCAGATGAAT ATAGGTAGTA GAACGGCAGA ACTAGTATTC AAAGCCAGGT CTGATGAATC	6095
15	CAAAAACAAA CACCCATTAC TCCCATTTTC TGGGACATAC TTACTCTACC CAGATGCTCT	6155
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	GTCTACTTAT ATATCTGTAT CTATCTCTTG CTTTGTTTCC AAAGGTAAAC TATGTGTCTA	6275
20	AATGTGGGCA AAAAATAACA CACTATTCCA AATTACTGTT CAAATTCCTT TAAGTCAGTG	6335
	ATAATTATTT GTTTTGACAT TAATCATGAA GTTCCCTGTG GGTACTAGGT AAACCTTTAA	6395
	TAGAATGTTA ATGTTTGTAT TCATTATAAG AATTTTTGGC TGTTACTTAT TTACAACAAT	6455
	ATTTCACTCT AATTAGACAT TTACTAAACT TTCTCTTGAA AACAATGCCC AAAAAAGAAC	6515
<i>2</i> 5	ATTAGAAGAC ACGTAAGCTC AGTTGGTCTC TGCCACTAAG ACCAGCCAAC AGAAGCTTGA	6575
	TTTTATTCAA ACTTTGCATT TTAGCATATT TTATCTTGGA AAATTCAATT GTGTTGGTTT	6635
	TTTGTTTTTG TTTGTATTGA ATAGACTCTC AGAAATCCAA TTGTTGAGTA AATCTTCTGG	6695
30	GTTTTCTAAC CTTTCTTTAG AT GTT ACC CTG TGT GAG GAG GCA TTC TTC AGG	6747
	Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg	
	180 185	
35	TTT GCT GTT CCT ACA AAG TTT ACG CCT AAC TGG CTT AGT GTC TTG GTA	6795
	Phe Ala Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val	
	190 195 200	
40		
	GAC AAT TTG CCT GGC ACC AAA GTA AAC GCA GAG AGT GTA GAG AGG ATA	6843
	Asp Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile	
	205 210 215	
45		
	AAA CGG CAA CAC AGC TCA CAA GAA CAG ACT TTC CAG CTG CTG AAG TTA	6891
	Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys Leu	
50	220 225 230 235	
	TGG AAA CAT CAA AAC AAA GAC CAA GAT ATA GTC AAG AAG ATC ATC CAA G	6940

Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile Ile Gln 240 245 250

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	TCAAATCTTG	CCCATAGGCA	AAGGGCAGTG	TCAAGTTTGC	CACTGAGATG	AAATTAGGAG	7240
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20	ATACAAAAAT	TAGCTGGGCA	TGGTAGCAGG	CACTTCTAGT	ACCAGCTACT	CAGGGCTGAG	7540
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	AGCCATTTTA	GCCTTTGCTT	TCTTATCTAA	AAAAAAAAA	AAAAAAATGA	AGGAAGGGGT	8140
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	TGGTTATTTT	CCTATGTAAT	GTCTACTTAT	ATATCTGTAT	CTATCTCTTG	CTTTGTTTCC	8500
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4 5	CAAATTCCTT	TAAGTCAGTG	TTTATTAATA	GTTTTGACAT	TAATCATGAA	GTTCCCTGTG	8620
	GGTACTAGGT	AAACCTTTAA	TAGAATGTTA	ATGTTTGTAT	TCATTATAAG	AATTTTTGGC	8680
	TGTTACTTAT	TTACAACAAT	ATTTCACTCT	AATTAGACAT	TTACTAAACT	TTCTCTTGAA	8740
50	AACAATGCCC	AAAAAAGAAC	ATTAGAAGAC .	ACGTAAGCTC	AGTTGGTCTC	TGCCACTAAG	8800
	ACCAGCCAAC	AGAAGCTTGA	TTTTATTCAA .	ACTTTGCATT	TTAGCATATT	TTATCTTGGA	8860
	AAATTCAATT	GTGTTGGTTT	TTTGTTTTTG	TTTGTATTGA	ATAGACTCTC	AGAAATCCAA	8920

	TTGTTGAGTA AATCTTCTGG GTTTTCTAAC CTTTCTTTAG AT ATT GAC CTC TGT Asp Ile Asp Leu Cys	3974
5	255	
		9022
10	Glu Asn Ser Val Gln Arg His Ile Gly His Ala Asn Leu Thr Phe Glu 260 265 270	
	CAG CTT CGT AGC TTG ATG GAA AGC TTA CCG GGA AAG AAA GTG GGA GCA	9070
15	Gln Leu Arg Ser Leu Met Glu Ser Leu Pro Gly Lys Lys Val Gly Ala	-
	275 280 285	
20		118
	Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys Lys Pro Ser Asp Gln Ile 290 295 300	
<i>2</i> 5	CTC AAC CTC CTC ACT TTC TCC CCA ATA AAA AA	
		166
	Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys Asn Gly Asp Gln Asp Thr 305 310 315 320	
30	305 310 315 320	
	TTG AAG GGC CTA ATG CAC GCA CTA AAG CAC TCA AAG ACG TAC CAC TTT 9	214
	Leu Lys Gly Leu Met His Ala Leu Lys His Ser Lys Thr Tyr His Phe	
35	325 330 335	
	CCC AAA ACT GTC ACT CAG AGT CTA AAG AAG ACC ATC AGG TTC CTT CAC 95	262
40	Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Thr Ile Arg Phe Leu His 340 345 350	
	AGC TTC ACA ATG TAC AAA TTG TAT CAG AAG TTA TTT TTA GAA ATG ATA 93	310
4 5	Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys Leu Phe Leu Glu Met Ile 355 360 365	
50		356
	Gly Asn Gln Val Gln Ser Val Lys Ile Ser Cys Leu	
	370 375 380	

5	TGGCCATTGA	GCTGTTTCCT	CACAATTGGC	GAGATCCCAT	GGATGAGTAA	ACTGTTTCTC	9416
	AGGCACTTGA	GGCTTTCAGT	GATATCTTTC	TCATTACCAG	TGACTAATTT	TGCCACAGGG	9476
	TACTAAAAGA	AACTATGATG	TGGAGAAAGG	ACTAACATCT	CCTCCAATAA	ACCCCAAATG	9536
	GTTAATCCAA	CTGTCAGATC	TGGATCGTTA	TCTACTGACT	ATATTTTCCC	TTATTACTGC	9596
	TTGCAGTAAT	TCAACTGGAA	ATTAAAAAAA	AAAAACTAGA	CTCCACTGGG	CCTTACTAAA	9656
10	TATGGGAATG	TCTAACTTAA	ATAGCTTTGG	GATTCCAGCT	ATGCTAGAGG	CTTTTATTAG	9716
	AAAGCCATAT	TTTTTTCTGT	AAAAGTTACT	AATATATCTG	TAACACTATT	ACAGTATTGC	9776
15	TATTTATATT	CATTCAGATA	TAAGATTTGG	ACATATTATC	ATCCTATAAA	GAAACGGTAT	9836
	GACTTAATTT	TAGAAAGAAA	ATTATATTCT	GTTTATTATG	ACAAATGAAA	GAGAAAATAT	9896
	ATATTTTAA	TGGAAAGTTT	GTAGCATTTT	TCTAATAGGT	ACTGCCATAT	TTTTCTGTGT	9956
20	GGAGTATTTT	TATAATTTTA	TCTGTATAAG	CTGTAATATC	ATTTTATAGA	AAATGCATTA	10016
	TTTAGTCAAT	TGTTTAATGT	TGGAAAACAT	ATGAAATATA	AATTATCTGA	ATATTAGATG	10076
	CTCTGAGAAA	TTGAATGTAC	CTTATTTAAA	AGATTTTATG	GTTTTATAAC	TATATAAATG	10136
	ACATTATTAA	AGTTTTCAAA	ATTTTTTATT	TTGCTTTCTC	TGTTGCTTTT	ATTT	10190

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Claims

- 30 1. A protein characterized by the following properties:
 - (a) molecular weights on SDS-polyacrylamide gel electrophoresis (SDS-PAGE)
 - ; approximately 60 kD under reducing conditions
 - ; approximately 60 kD and 120 kD under non-reducing conditions
 - (b) a high affinity to cation-exchange column and heparin column
 - (c) a biological activity to inhibit osteoclast differentiation and/or maturation
 - ; its activity is decreased by heating at 70°C for 10 min or at 56°C for 30 min.
 - ; its activity is lost by heating at 90 °C for 10 min
 - (d) internal amino acid sequences provided in sequence numbers 1, 2, and 3.
- 45 2. A protein of claim 1 having N-terminal amino acid sequences provided in sequence number 7.
 - 3. A protein of claim 1 produced in human fibroblasts.
- 4. A method of producing the protein of claim 1, 2, and 3 by the following process: cultivating human fibroblasts; purifying the protein by a combination of ion-exchange column, affinity-column and reverse phase-column chromatography.
 - 5. A method of producing the protein of claim 4 by cultivating human fibroblasts on alumina ceramic pieces.
- 6. A protein with amino acid sequence provided in sequence number 4.
 - 7. cDNAs encoding amino acid sequence provided in sequence number 4.

8. cDNA with nucleotide sequence provided in sequence number 6.

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- 9. cDNAs that hybridize to cDNA provided in sequence number 6 under moderately stringent conditions.
- 10. A protein expressed from cDNA encoding amino acid sequence provided in sequence number 4.
 - 11. A protein with a biological activity to inhibit osteoclast differentiation and/or maturation, that obtain as amino acid expressed cDNA sharing at least 80 % sequence identity with the amino acid sequence provided in sequence number 4.
 - 12. A method of production of the protein with the following properties and inhibit osteoclast differentiation and/or maturation by gene engineering using cDNA encoding amino acid sequence provided in sequence number 4:
 - (a) molecular weights on SDS-polyacrylamide gel electrophoresis (SDS-PAGE)
 - ; approximately 60 kD under reducing conditions
 - ; approximately 60 kD and 120 kD under non-reducing conditions
 - (b) a high affinity to cation-exchange column and heparin column
 - (c) ; inhibit osteoclast differentiation and/or maturation activity is decreased by heating at 70°C for 10 min or at 56°C for 30 min
 - ; its activity is lost by heating at 90 °C for 10 min
 - (d) internal amino acid sequence provided in sequence number 1-3.
 - 13. A method of producing the protein according to claim 10 by gene engineering using mammalian cells as host cells.
- 14. A method of producing the protein according to claim 13 by gene engineering using 293/EBNA cells or CHO cells30 as mammalian host cells.
 - 15. A cDNA with nucleotide sequence provided in sequence number 8.
 - 16. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 8.
 - 17. cDNAs encoding amino acid sequence provided in sequence number 9.
 - 18. A cDNA with nucleotide sequence provided in sequence number 10.
- 40 19. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 10.
 - 20. cDNAs encoding amino acid sequence provided in sequence number 11.
 - 21. A cDNA with nucleotide sequence provided in sequence number 12.
 - 22. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 12.
 - 23. cDNAs encoding amino acid sequence provided in sequence number 13.
- 50 24. A cDNA with nucleotide sequence provided in sequence number 14.
 - 25. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 14.
 - 26. cDNAs encoding amino acid sequence provided in sequence number 15.
 - 27. A cDNA with nucleotide sequence provided in sequence number 83.
 - 28. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 83.

- 29. cDNAs encoding amino acid sequence provided in sequence number 62.
- 30. A cDNA with nucleotide sequence provided in sequence number 84.
- A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 84.
 - 32. cDNAs encoding amino acid sequence provided in sequence number 63.
 - 33. A cDNA with nucleotide sequence provided in sequence number 85.

34. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 85.

- 35. cDNAs encoding amino acid sequence provided in sequence number 64.
- 36. A cDNA with nucleotide sequence provided in sequence number 86.
 - 37. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 86.
 - 38. cDNAs encoding amino acid sequence provided in sequence number 65.
 - 39. A cDNA with nucleotide sequence provided in sequence number 87.

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- 40. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 87.
- 25 41. cDNAs encoding amino acid sequence provided in sequence number 66.
 - 42. A cDNA with nucleotide sequence provided in sequence number 88.
 - 43. A protein encoded by a cDNA having a sequence provided in sequence number 88.
 - 44. cDNAs encoding amino acid sequence provided in sequence number 67.
 - 45. A cDNA with nucleotide sequence provided in sequence number 89.
- 35 46. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 89.
 - 47. cDNAs encoding amino acid sequence provided in sequence number 68.
 - 48. A cDNA with nucleotide sequence provided in sequence number 90.
 - 49. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 90.
 - 50. cDNAs encoding amino acid sequence provided in sequence number 69.
- 45 51. A cDNA with nucleotide sequence provided in sequence number 91.
 - 52. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 91.
 - 53. cDNAs encoding amino acid sequence provided in sequence number 70.
 - 54. A cDNA with nucleotide sequence provided in sequence number 92.
 - 55. A protein encoded by a cDNA having a nucleotide sequence provided in number 92.
- 55 56. cDNAs encoding amino acid sequence provided in sequence number 71.
 - 57. A cDNA with nucleotide sequence provided in sequence number 93.

- A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 93.
- 59. cDNAs encoding amino acid sequence provided in sequence number 72.
- 60. A cDNA with nucleotide sequence provided in sequence number 94.
 - 61. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 94.
 - 62. cDNAs encoding amino acid sequence provided in sequence number 73.
 - 63. A cDNA with nucleotide sequence provided in sequence number 95.

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- 64. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 95.
- 15 65. cDNAs encoding amino acid sequence provided in sequence number 74.
 - 66. A cDNA with nucleotide sequence provided in sequence number 96.
 - 67. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 96.
 - 68. cDNAs encoding amino acid sequence provided in sequence number 75.
 - 69. A cDNA with nucleotide sequence provided in sequence number 97.
- 25 70. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 97.
 - 71. cDNAs encoding amino acid sequence provided in sequence number 76.
 - 72. A cDNA with nucleotide sequence provided in sequence number 98.
 - 73. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 98.
 - cDNAs encoding amino acid sequence provided in sequence number 77.
- 75. A cDNA with nucleotide sequence provided in sequence number 99.
 - 76. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 99.
 - 77. cDNAs encoding amino acid sequence provided in sequence number 78.
 - 78. A cDNA with nucleotide sequence provided in sequence number 100.
 - 79. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 100.
- 45 80. cDNAs encoding amino acid sequence provided in sequence number 79.
 - 81. A cDNA with nucleotide sequence provided in sequence number 101.
 - 82. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 101.
 - 83. cDNAs encoding amino acid sequence provided in sequence number 80.
 - 84. A cDNA with nucleotide sequence provided in sequence number 102.
- 85. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 102.
 - 86. cDNAs encoding amino acid sequence provided in sequence number 81.

- 87. A cDNA with nucleotide sequence provided in sequence number 103.
- 88. A protein encoded by a cDNA having a nucleotide sequence provided in sequence number 103.
- 89. cDNAs encoding amino acid sequence provided in sequence number 82.
 - 90. Genomic DNAs encoding the amino acid sequence provided in sequence number 4.
 - 91. Genomic DNAs of Claim 90 with the nucleotide sequence provided in sequence number 104 or 105.
 - 92. An antibody having specific affinity to the OCIF
 - 93. An antibody of Claim 92 that is polyclonal antibody.
- 94. An antibody of Claim 92 that is monoclonal antibody.

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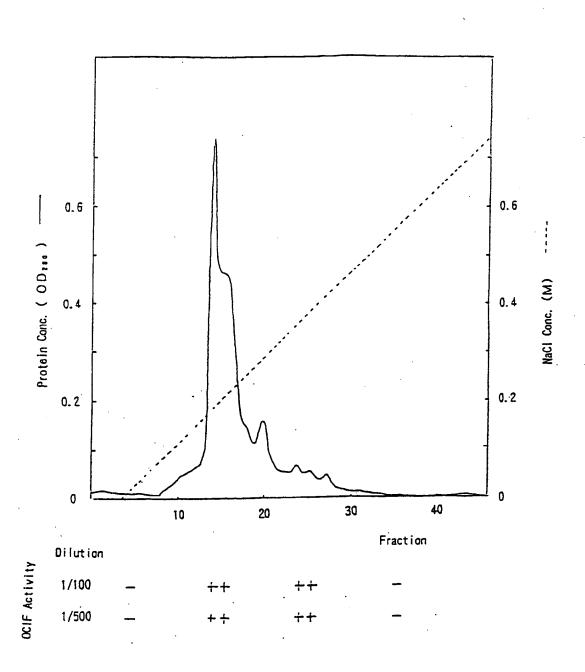
45

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- 95. A monoclonal antibody of Claim 94 being characterized by the following properties. Molecular weight of about 150,000, and of subclass $\lg G_1$, $\lg G_{2a}$, or $\lg G_{2b}$.
- 96. A method of determining the concentration of the protein of the OCIF using the antibodies of Claim 92, 93, 94, and 95.

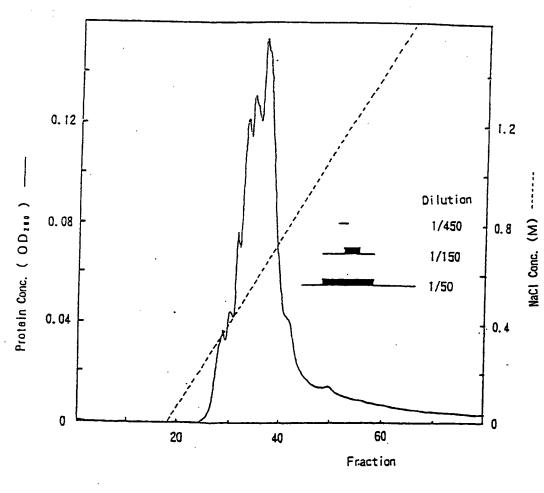
4.7

Fig. 1



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Fig. 2



OCIF Activity +: --- , ++:

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Fig. 3

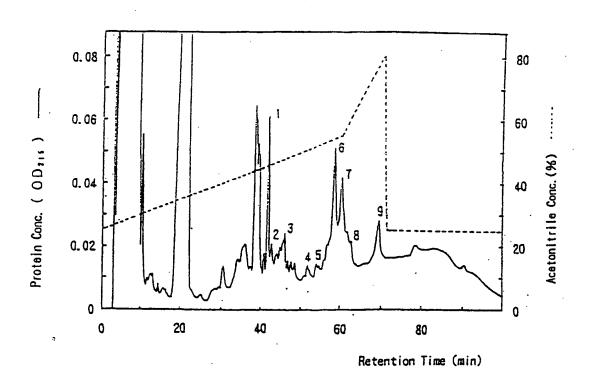
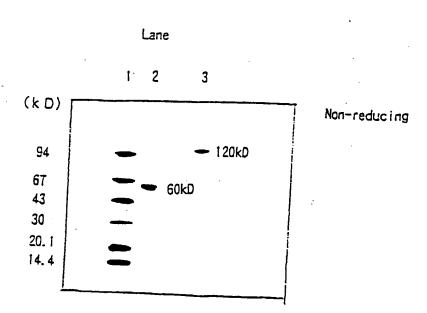
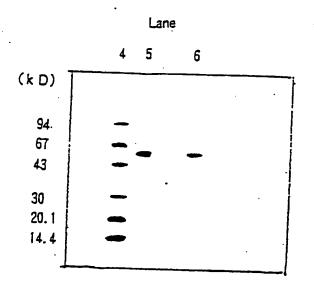


Fig. 4





Reducing .

Fig.5

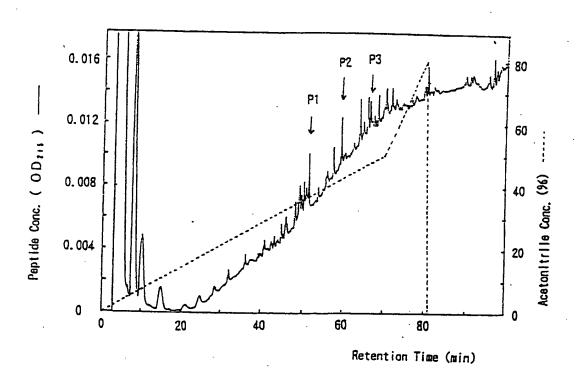


Fig. 6

Lane

1 2 3 4 5 6 7

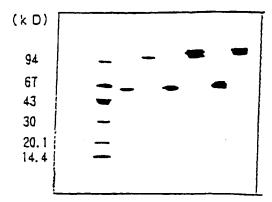


Fig. 7

Lane

8 9 10 11 12 13 14

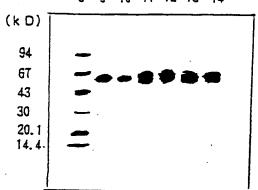


Fig.8

Lane

15 16 17 18 19 20 21

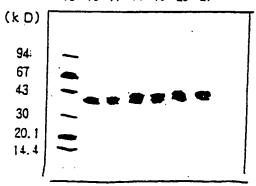


Fig. 9

•	1 MNNLLCCALVFLDISIKWTTQETFPPKYLHYDEETSHQLLCDX	KCPPGTYL	КОНСТАКМКТ	(00774
				,
	MNNLLCCALVFLDISIKWTTQETFPPKYLHYDEETSHQLLCDK	KCPPGTYLI	KOHCTAKWKT	(OCIF2
	61 VCAPCPOHYYTDSWHTSDECLYCSPVCKELQYVKQECNRTHNR			
	VCAPCPDHYYTDSWHTSDECLYCSPVCKECNRTHNR	RVCECKEGR	YLEIEFCLK	(OCIF2)
	121			
	HRSCPPGFGVVQAGTPERNTVCKRCPDGFFSNETSSKAPCRKHT	TNCSVFGL	LLTOKGNAT	(OCIF1)
	HRSCPPGFGVVQAGTPERNTVCKRCPDGFFSNETSSKAPCRKHT	TNCSVFGL	LLTOKGNAT	(OCIF2)
	181			
	HDNICSGNSESTQKCGIDVTLCEEAFFRFAVPTKFTPNWLSVLV	**++++		(OCIF1)
1	HDNICSGNSESTQKCGIDVTLCEEAFFRFAVPTKFTPNWLSVLV	/DNLPGTĶ1	MAESVERI	(OCIF2)
:	241			
	KRQHSSQEQTFQLLKLWKHQNKDQDIVKKIIQDIDLCENSVQRH	*****	****	(OCIF1)
2	KRQHSSQEQTFQLLKLWKHQNKDQDIVKKIIQDIDLCENSVQRH 234	IIGHANLTF	EQLRSLME	(OCIF2)
3	301			
	SLPGKKYGAEDIEKTIKACKPSDQILKLLSLWRIKNGDQDTLKGI	*****		(OCIF1)
2	SLPGKKVGAEDIEKTIKACKPSDQILKLLSLWRIKNGDQDTLKGU 294	LMHALKHS	KTYHFPKT (OCIF2)
	361			
	**************	OCIF1)		
۷ 3	TQSLKKTIRFLHSFTMYKLYQKLFLEMIGNQVQSVKISCL (0 154	OCIF2)		

Fig. 10

1	
MNNLLCCALVFLDISIKWTTQETFPPKYLHYDEETSHQL	
MNKLLCCALVFLDISIKWTTQETFPPKYLHYDEETSHQL I	LCDKCPPGTYLKQHCTAKWKT (OCIF3
61	
VCAPCPDHYYTDSWHTSDECLYCSPVCKELQYVKQECNRT	· * * * * * * * * * * * * * * * * * * *
VCAPCPDHYYTDSWHTSDECLYCSPVCKELQYVKQECNR1 61	THNRVCECKEGRYLEIEFCLK (OCIF3
121	
frscppgfgvvqagtperntvckrcpdgffsnetsskapc	******
HRSCPPGFGVVQAGTPERNTVCKRCPDGFFSNETSSKAPC 121	RKHTNCSVFGLLLTQKGNAT (OCIF3)
.81	
DNICSGNSESTQKCGIDVTLCEEAFFRFAVPTKFTPNWL	SVLVDNLPGTKVNAESVERI (OCIF1)
DNICSGNSESTQKCGIDVTLCEEAFFRFAVPTKFTPNWL: 81	SYLVDNLPGTKYNAESVERI (OCIF3)
41	•
RQHSSQEQTFQLLKLWKHQNKDQDIVKKIIQDIDLCENS\	/QRHIGHANLTFEQLRSLME (OCIF1)
RQHSSQEQTFQLLKLWKHQNKDQDIVKKIIQDIDLCENS\ 41	/QRHIGHANLS (OCIF3)
01	
LPGKKYGAEDIEKTIKACKPSDQILKLLSLWRIKNGDQDT	LKGLMHALKHSKTYHFPKT (OCIFI)
	LKGLMHALKHSKTYHFPKT (OCIF3)
51	
「QSLKKTIRFLHSFTMYKLYQKLFLEMIGNQVQSVKISCL	(OCIF1)
TQSLKKTIRFLHSFTMYKLYQKLFLEMIGNQVQSVKISCL	(OCIF3)

. . .

Fig. 11

1 MNNLLCCALYFLDISIKWTTQETFPPKYLHYDEETSHQLLCDKCPPGTYLKQHCTAKWKT ** **** *****************************	
61 VCAPCPDHYYTDSWHTSDECLYCSPVCKELQYVKQECNRTHNRVCECKEGRYLEIEFCLK ************************************	•
121 HRSCPPGFGVVQAGTPERNTVCKRCPDGFFSNETSSKAPCRKHTNCSVFGLLLTQKGNAT ************************************	(OCIF1)

Fig. 12

1	
MNNLLCCALYFLDISIKWTTQETFPPKYLHYDEETSHQLLCDKCPPGTYLKQHCTAKWKT	. •
MNKLLCCALVFLDISIKWTTQETFPPKYLHYDEETSHQLLCDKCPPGTYLKQHCTAKWKT	(OCIFS)
51	•
CAPCPDHYYTDSWHTSDECLYCSPVCKELQYVKQECNRTHNRVCECKEGRYLEIEFCLK	•
CAPCPDHYYTDSWHTSDECLYCSPYCKELQYYKQECHRTHHRYCECKEGRYLEIEFCLK	(OCIF5)
21	
RSCPPGFGVVQAGTPERNTVCKRCPDGFFSNETSSKAPCRKHTNCSVFGLLLTQKGNAT	(OCIF1)
RSCPPGFGVVQAGCRRPKPQICI 21	(OCIF5)

Fig. 13

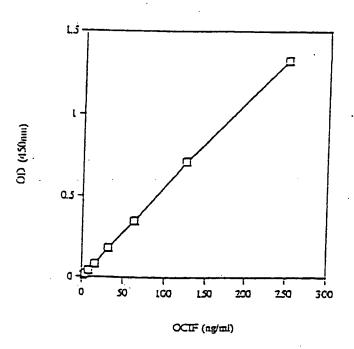


Fig.

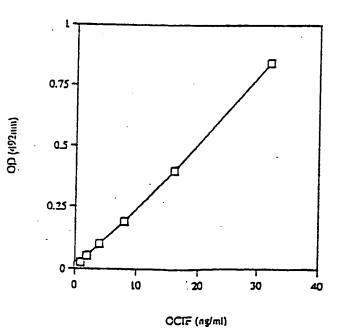
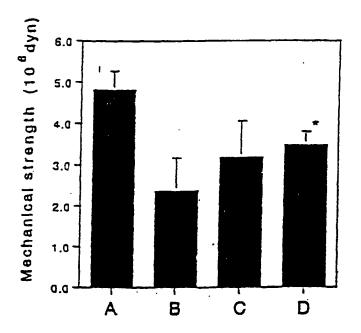


Fig. 15



A: Normal rat

B : Denerved rat + Vehicle

C: Denerved rat + OCIF 10 µg/kg/day

C: Denerved rat + OCIF 100 µg/kg/day

INTERNATIONAL SEARCH REPORT International application No. PCT/JP96/00374 CLASSIFICATION OF SUBJECT MATTER Int. C16 C07K14/52, C07K16/24, C12N15/19, C12N15/06, C12N5/08, C12N5/10, C12N5/20, C12P21/02, C12P21/08, G01N33/577 According to International Patent Classification (IPC) or to both national classification and IPC FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07K14/52, C07K16/24, C12N15/19, C12N15/06, C12N5/08, C12N5/10, C12N5/20, C12P21/02, C12P21/08, G01N33/577 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) BIOSIS PREVIEWS, CAS ONLINE, WPI, WPI/L C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Category* Relevant to claim No. Fawthrop, F.W. et al. "The effect of 1 - 96transforming growth factor beta on the plasminogen activator activity of normal human osteoblast-like cells and a human osteosacroma cell line MG-63", J. Bone. Miner. Res. (1992) Vol. 7, No. 12, p. 1363-1371 A Fenton, A.J. et al. "Long-term culture of 1 - 96 disaggregated rat osteoclasts inhibition of bone resorption and reduction of osteoclastlike cell number by calcitonin and PTHrP107-139", J. Cell Physiol. (1993) Vol. 155, No. 1, p. 1-7 Further documents are listed in the continuation of Box C. See patent family annex. Special categories of cited documents: later document published after the international filing date or priority date and not in conflict with the application but cited to understand document defining the general state of the art which is not consid-to be of particular relevance -Athe principle or theory underlying the inve "E" earlier document but published on or after the International Illing date "X" document of particular relovance; the claimed inventor cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relovance; the claimed invention cast considered to involve an inventive step when the docume combined with one or more other such documents, such combi-bring obvious to a person skilled in the art "O" document referring to an oral disclosure, use, exhibition or other document published prior to the international filing date but later than the priority date claimed "A" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report May 14, 1996 (14. 05. 96) May 28, 1996 (28. 05. 96) Name and mailing address of the ISA/ Authorized officer Japanese Patent Office Facsimile No. Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

binant plasmid containing the 5.8 kb EcoRI/NotI fragment was isolated and this plasmid was termed pBSG8-5.8. pBSG8-5.8 was digested with HindIII and 0.9 kb of DNA fragment derived from this digestion was isolated in the same manner as described above. This 0.9 kb fragment was then doned in pBluescript II SK- at the HindIII site as described above. This recombinant plasmid containing 0.9 kb HindIII fragment was denoted pBS8H0.9.

λOIF11 DNA was digested with EcoRI and 6 kb, 3.6 kb, 2.6 kb EcoRI fragments were isolated in the same manner as described above and doned in pBluescript II SK+ vector at the EcoRI site as described above. These recombinant plasmids were termed pBSG11-6, pBSG11-3.6, and pBSG11-2.6, respectively. pBSG11-6 was digested with HindIII and the digest was applied on a 0.7 % agarose gel. Three fragments, 2.2 kb, 1.1 kb, and 1.05 kb in length, were extracted from the gel and cloned independently in pBluescript II SK- vector at the HindIII site in the same manner as described above. These recombinant plasmids were termed pBS6H2.2, pBS6 H1.1 and pBS6H1.05, respectively.

The nucleotide sequence of the cloned genomic DNA was determined using ABI Dyedeoxy Terminator Cycle Sequencing Ready Reaction Kit (PERKIN ELMER) and 373A DNA Sequencing system (Applied Biosystems). Plasmids pBSG8-5.8, pBS8H0.9, pBSG11-6, pBSG11-3.6, pBSG11-2.6, pBSGH2.2, pBS6H1.1 and pBS6H1.05 were prepared according to the alkaline-SDS procedure as described in Molecular Cloning: A Laboratory Manual and used as templates for the DNA sequence analysis. Nucleotide sequence of the human OCIF gene was presented in Sequence No 104 and Sequence No 105. The nucleotide sequence of the DNA, between exon 1 and exon 2 was not entirely determined. There is a stretch of approximately 17 kb of nucleotides between the sequences given in sequence No. 104 and sequence No. 105.

20 EXAMPLE 24

Quantitation of OCIF by EIA

i) Preparation of anti-OCIF antibody

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Male JW rabbits (Kitayama LABES Co., LTD) weighing 2.5-3.0 kg were used for immunization for preparing antisera. Three male JW rabbits (Kitayama LABES Co., LTD) weighing 2.5-3.0 kg were used for immunization. For immunization, emulsion was prepared by mixing an equal volume of rOCIF (200 µg/ml) and complete Freund's adjuvant (Difco, Cat. 0638-60-7). The rabbits were immunized subcutaneously six times at the interval of one week with 1 ml of emulsion per injection. The rabbits were injected six times at the interval of seven days subcutaneously. Whole blood was obtained ten days after the final immunization and serum was separated. Antibody was purified from serum as follows. Antiserum was diluted two-fold with PBS. After adding ammonium sulfate at a final concentration of 40 w/v %, antiserum was allowed to stand at 4 °C for 1 hr.. Precipitate obtained by centrifugation at 8000 x g for 20 min. was dissolved in a small volume of PBS and was dialyzed against PBS. The resulting solution was loaded onto a Protein G-Sepharose column (Pharmacia). After washing with PBS, absorbed immunoglobulin G was eluted with 0.1 M glycine-HCL buffer (pH 3.0). Elutes were neutralized with 1.5 M Tris-HCL buffer (pH 8.7) immediately and were dialyzed against PBS. Protein concentration was determined by absorbance at 280nm (E^{1%} 13.5).

Horseradish peroxidase labeled antibody was prepared using ImmunoPure Maleimide Activated Horseradish Peroxidase Kit (Pierce, Cat. 31494). Briefly, one mg of IgG was incubated with 80 ug of N-succinimidyl-S-acetylthioacetate for 30 min. After deacetylation with 5 mg of hydroxylamine HCl, modified IgG was separeted by polyacrylamide desalting column. Protein pool mixed with one mg of maleimide activated horseradish peroxidase was incubated at room temperature for 1 hr.

ii) Quantitation of OCIF by sandwich EIA

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Microtiter plates (Nunc MaxiSorp Immunoplate) were coated with rabbit anti-OCIF IgG by incubating 0.2 ug in 100 ul of 50 mM sodium bicarbonate buffer pH 9.6 at 4C overnight. After blocking the plates by incubating for 1 hour at 37°C with 300 ul of 25% BlockAce/PBS (Snow Brand Milk Products), 100ul of samples were incubated for 2 hours at room temperature. After washing the plates three times with PBST (PBS containing 0.05% Tween20), 100 ul of 1:10000 diluted horseradish peroxidase labeled anti-OCIF IgG was added and incubated for 2 hours at room temperture. The amount of OCIF was determined by incubation with 100 ul of a substrate solution (TMB, ScyTek Lab., Cat. TM4999) and measurement of the absorbance at 450 nm using an ImmunoReader (Nunc NJ2000). Purified recombinant OCIF was used as a standard protein and a typical standared curve was shown in Fig. 13.

EXAMPLE 25

Anti-OCIF monoclonal antibody

i) Preparation of hybridoma producing anti-OCIF monoclonal antibody.

OCIF was purified to homogeneity from culture medium of human fibroblasts, IMR-90 by the purification method described in Eample 11. Purified OCIF was dissolved in PBS at a concentration of 10 μ g/100 μ l. BALB/c mice were immunized by administrating this solution intraperitoneally three times every two weeks. In the first and the second immunizations, the emulsion composed of an equal volume of OCIF and Freund's complete adjuvant was administrated. Three days after the final administration, the spleen was taken out, lymphocytes were isolated and fused with mouse myeloma p3x63-Ag8.653 cells according to the conventinal method using polyethyleneglycol. Then the fused cells were cultured in HAT medium to select hybridoma. Subsequently, to check whether the selected hybridomas produce anti-OCIF antibody, anti-OCIF antibody in each culture medium of hybridomas was determined by solid phase ELISA which was prepared by coating each well in 96-well immunoplates (Nunc) with 100 μ l of purified OCIF (10 μ g/ml in 0.1 M NaHCO₃) and by blocking each well with 50% BlockAce (Snow Brand Milk Products Co. Ltd.). The hybridoma clones secreting anti-OCIF antibody were established by cloning 3 - 5 times by limit dilution and by screening using the above solid phase ELISA. Among thus obtained hybridoma clones, several hybridoma clones with high production of anti-OCIF antibody were selected.

ii) Production of anti-OCIF monoclonal antibodies.

Each hybridoma clone secreting anti-OCIF antibody, which was obtained in EXAMPLE 25-i), was transplanted intraperitoneally to mice given Pristane (Aldrich) at a cell density of 1 x 10⁶ cells/mouse. The accumulated ascites was collected 10 - 14 days after the transplantation and the ascites containing anti-OCIF specific monoclonal antibody of the present invention was obtained. Purified antibodies were obtained by Affigel protein A Sepharose chromatography (BioRad) according to the maufacturer's manual. That is, the ascites was diluted with equal volume of a binding buffer (BioRad) and applied to protein A column. The column was washed with a sufficient volume of the binding buffer and eluted with an elution buffer (BioRad). After neutralizing, the obtained eluate was dialyzed in water and subsequently lyophilized. The purity of the obtained antibody was analyzed by SDS/PAGE and a homogenous band with a molecular weight of about 150,000 was detected.

iii) Selection of monoclonal antibody having high affinity to OCIF

Each antibody obtained in EXAMPLE 25-ii) was dissolved in PBS and the concentration of protein in the solution was determined by the method of Lowry. Each antibody solution with the same concentration was prepared and then serially diluted with PBS. Monoclonal antibodies, which can recognize OCIF even at highly diluted solution, were selected by solid phase ELISA described in EXAMPLE 25-ii). Thus three monoclonal antibodies A1G5, E3H8 and D2F4 can be selected.

iv) Determination of class and subclass of antibodies

The class and subclass of the antibodies of the present invention obtained in EXAMPLE 25-iii) were analyzed using an immunoglobulin class and subclass analysis kit (Amersham). The procedure was carried out according to the protocol disclosed in the directions. The results were shown in Table 15. The antibodies of the present invention, E3H8, A1G5 and D2F4 belong to $\lg G_{2a}$ and $\lg G_{2b}$, respectively.

Table 15

Analysis of class and subclass of the antibodies in the present invention.							
Antibody	lgG ₁	lgG _{2a}	lgG _{2b}	lgG ₃	IgA	lgM	κ
A1G5	-	+	•	-	-	-	+
E3H8	+	-	-	-	-	-	+
D2F4	-	-	+	-	-	-	+

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v) Determination of OCIF by ELISA

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Three kinds of monoclonal antibodies, A1G5, E3H8 and D2F4, which were obtained in EXAMPLE 25-iv), were used as solid phase antibodies and enzyme-labeled antibodies, respectively. Sandwich ELISA was constructed by each combination of solid phase antibody and labeled antibody. The labeled antibody was prepared using Immuno Pure Maleimide Activated Horseradish Peroxidase Kit (Pierce, Cat. No. 31494). Each monoclonal antibody was dissolved in 0.1 M NaHCO₃ at a concentration of 10 µg/ml, and 100 µl of the solution was added to each well in 96-well immunoplates (Nunc, MaxiSorp Cat. No. 442404) followed by allowing to stand at room temperature overnight. Subsequently, each well in the plates was blocked with 50% Blockace (Snow Brand Milk Products, Co. , Ltd.) at room temperature for 50 minutes, and then was washed three times with PBS containing 0.1% Tween 20 (washing buffer).

A series of concentrations of OCIF was prepared by diluting OCIF with 1st reaction buffer (0.2 M Tris-HCl bufer, pH 7.4, containing 40% Blockace and 0.1% Tween 20). Each well in 96-well immunoplates was filled with 100µl of the prepared OCIF solution with each concentration, allowed to stand at 37 °C for 3 hours, and subsequently washed three times with the washing buffer. For dilution of POD-labeled antibody, 2nd reaction buffer (0.1 M Tris-HCl buffer, pH 7.4, containing 25% Blockace and 0.1% Tween 20) was used. POD-labeled antibody was diluted 400-fold with 2nd reaction buffer, and 100 µl of the diluted solution was added to each well in the immunoplates. Each imunoplate was allowed to stand at 37 °CC for 2 hours, and subsequently washed three times with the washing buffer. After washing, 100 µl of a substrate solution (0.1 M citrate-phosphate buffer, pH 4. 5, containing 0.4 mg/ml of o-phenylenediamine HCl and 0.006% H₂O₂) was added to each well in the immunoplates and the immunoplates were incubated at 37°C for 15 min. The enzyme reaction was terminated by adding 50 µl of 6 N H₂SO₄ to each well. The optical density of each well was determined at 492 nm using an immunoreader (ImmunoReader NJ 2000, Nunc).

Using three kinds of monoclonal antibody in the present invention, each combination of solid phase and POD-labeled antibodies leads to a accurate determination of OCIF. Each monoclonal antibody in the present invention was confirmed to recognize a different epitope of OCIF. A typical standard curve of OCIF using a combination of solid phase antibody, A1G5 and POD-labeled antibody, E3H8 was shown in Fig. 14.

vi) Determination of OCIF in human serum

Concentration of OCIF in five samples of normal human serum was determined using an EIA system described in EXAMPLE 25-v). The immunoplates were coated with A1G5 as described in EXAMPLE 25-v), and 50 µl of 1st. reaction buffer was added to each well in the immunoplates. Subsequently, 50µl of each human serum was added to each well in the immunoplates. The immunoplates were incubated at 37°C for 3 hours and then washed three times with the washing buffer. After washing, each well in the immunoplates was filled with 100µl of POD-E3H8 antibody diluted 400-fold with 2nd. reaction buffer and incubated at 37°C for 2 hours. After washing the immunoplates three times with the washing buffer, 100 µl of the substrate solution described in EXAMPLE 25-v) was added to each well and incubated at 37°C for 15 min. The enzyme reaction was terminated by adding 50 µl of 6 N H₂SO₄ to each well in the immunoplates. The optical density of each well was determined at 492 nm using an immunoreader (ImmunoReader NJ 2000, Nunc). 1st. reaction buffer containing the known amount of OCIF was treated in the same way and a standard curve of OCIF as shown in fig. 2 was obtained. Using the standard curve of OCIF, the amount of OCIF in human serum sample was determined. The results were shown in Table 14.

Table 14

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The amount of OCIF in normal human serum			
Serum Sample	OCIF Concentration (ng/ml)		
1	5.0		
2	2.0		
3	1.0		
4	3.0		
5	1.5		